IRB-SB approval is effective from date of this notice and good for the date indicated. Reviews are required to keep project active.

UNIVERSITY OF CALIFORNIA, RIVERSIDE
IRB Socio-Behavioral (IRB-SB)
Office of Research Integrity
July 20, 2016

APPROVAL NOTICE

INVESTIGATOR: Reynolds, Chandra **Faculty Advisor:** N/A

ACADEMIC UNIT: Psychology **Administrator:** N/A

PROJECT TITLE: "Colorado Adoption/Twin Study of Lifespan Behavioral Development & Cognitive Aging (CATSLife)"

IRB-SB. NUMBER: **HS - 14-073** **PROJECT PERIOD: 9/01/2014 - 8/30/2019**

APPROVAL DATE: July 20, 2016 **EXPIRATION DATE: July 19, 2017**

FUNDING SOURCE: NIA 1R01AG046938

SPECIAL CONDITIONS: None

THE UCR IRB-SB HAS REVIEWED THE PROPOSED USE OF HUMAN PARTICIPANTS IN THE REFERENCED APPLICATION AND APPROVED IT BASED ON THE FOLLOWING DETERMINATIONS:

1. Level of Review - 45 CFR 46.101(b)(4) Exempt
2. Special Population - None
3. Risk - Minimal
4. The risks to participants are minimized by using procedures consistent with sound research design that do not unnecessarily expose participants to risk.
5. The risks are reasonable in relation to the anticipated benefits to individual participants and the importance of the knowledge that may reasonably be expected to result.
6. The selection of participants is reasonable and equitable.
7. The PI has had the appropriate human subjects research training.
8. Consent - Existing Data - Waived per 45 CFR 46.116(d)

Once the special conditions, if any, have been met, the protocol will be approved *through* July 19, 2017.

A "Continuing Review of the Approved Human Subjects Protocol" form will be sent to the PI three months before the expiration date, which will allow the PI to indicate whether to keep the application active or not. Please note that the expiration date is the last date that the application is approved.

THE INVESTIGATOR SHALL PROMPLTY REPORT THE FOLLOWING TO THE IRB-SB:
(1) Changes to the application (e.g., increase the number of participants, or changing the participant population, recruitment methods, procedures, documents) via an amendment, or
(2) Unanticipated problems involving risk to participants or others (please contact the IRB-SB for instructions).

DATE APPROVED July 20, 2016

DR. DERICK FAY, CHAIR, IRB-SB
DESIGNATED UCR IRB-SB MEMBER
DR. MICHAEL PAZZANI (UCR IO), VICE CHANCELLOR, RESEARCH

APPLICATION TO EXTEND APPROVAL TO AN EXISTING HUMAN PARTICIPANTS APPLICATION

This form MUST be received and approved by July 19, 2016 or your application will automatically expire and all research activities must crease, including the enrollment of new participants.

APPROVED

PI: **Reynolds, Chandra**
Protocol: **HS-14-073** Level of Review: **45 CFR 46.101(b)(4) Exempt**
Project Title(s): **"Colorado Adoption/Twin Study of Lifespan Behavioral Development & Cognitive Aging (CATSLife)"**

Received / Reviewed 7/19/16 KRC

Indicate the status of your study and answer the questions below:

A. _____ Recruitment has not yet began.

B. _____ Data collection procedures are complete, analyzing identifiable data.

C. X The project is active and data collection is not completed.

D. _____ On hold. Elaborate _____.

1. Please indicate the number of participants recruited in the last year: 254. If none, briefly explain why:
_____

2. Please indicate the total number of participants recruited since the beginning of the study: 254. *(Please Note: If this number is more than what was originally approved, an amendment should have been filed and approved. If that did not happen, please contact the ORI.)*

For questions 3-11, please answer **yes** or **no** (***if any are Yes, please provide a summary***):

Yes (**No**) **3.** Since the last IRB review, have participants experienced any untoward effects or outcomes?

(**Yes**) **No** **4.** Since the last IRB review, have you deviated in any way from your approved IRB application (and/or) amendments)? CU Boulder site updated their protocol, with minor changes to measures. No impact to UCR, given de-identified data.

Yes (**No**) **5.** Since the last IRB review, have there been any adverse events or unanticipated problems involving risks to participants or others?

Yes (**No**) **6.** Since the last IRB review, have any participants or others complained about or withdrawn consent from the research? If yes, please state how many and why on a separate sheet.

Yes (**No**) **8.** Since the last IRB review, has there been any other relevant information regarding this research, especially information about risks associated with the research?

Yes (**No**) **9.** In your opinion, have the risks or potential benefits of this research changed?

Yes (**No**) **10.** Since the last IRB review, have you receive funding from any agencies other than what has already been indicated (~~NIA/NIH~~)?NIA funding was indeed received, start date 6/1/2015

Yes (**No**) **11.** Since the last IRB review, has there been any change that would create (or eliminate) a financial conflict of interest related to this application? If the answer is yes or you are unsure, please contact the Office of Research Integrity.

12. Project Roster - a current research personnel roster is required, please see attached. [see additions]

13. Indicate funding source and grant number: NIA 1R01AG046938

Chandra A. Reynolds 06/13/2016
Principal Investigator Date

7/19/16
Designated UCR IRB-SB member or staff Date

_____
Faculty Advisor Date

****Faculty Advisor: Please check here (and sign above) if the PI is no longer affiliated with UCR ____**

PROJECT ROSTER:

PI: **Reynolds, Chandra**
Protocol: **HS-14-073** Level of Review: **45 CFR 46.101(b)(4) Exempt**
Project Title(s): **"Colorado Adoption/Twin Study of Lifespan Behavioral Development & Cognitive Aging (CATSLife)"**

UCR requires that all investigators, student employees, post-doctoral researchers, staff research associates, post-graduate researchers and technicians who works experimentally on the IRB application be in compliance with UCR SOP Section 13.10, "Training/Ongoing Education of Principal Investigator and Research Team", and specifically subsection "Continuing Education and Recertification".

The principal investigator is responsible for keeping this roster current and ensuring that all research personnel have completed the UCR Human Subjects Tutorial within the last five years. The UCR Human Subjects Tutorial can be found at: http://research.ucr.edu/OrApps/RI/Training/Tutorial/Default.aspx.

If the roster includes a research assistant or collaborator who has completed a similar tutorial elsewhere, a copy of that institution's certification must be submitted. This certification will only be valid at UCR for five years, after which the UCR Human Subjects tutorial will need to be completed and its certification submitted to the Office of Research Integrity.

INSTRUCTIONS: Based on your last submission, the names below are listed in our database as "key personnel" involved on your application. Please amend the list as needed to add or subtract personnel from this project and send this form back with your renewal. It will be checked against the master database and should anyone on it be required to take or re-take the tutorial, you will be notified.

Reynolds, Chandra - 6/27/2014
Bannon, Brittany - 9/22/2011
Phillips, Dianna - 10/20/2013
Paige Trubenstein, Brittany - 9/29/2015
Rodriguez Staben, Omar - 1/9/2015
Trinh, Nhu (Lily) - 7/27/2015
Munoz Diaz, Elizabeth - 6/14/2015

University of Colorado Boulder

Institutional Review Board
563 UCB
Boulder, CO 80309
Phone: 303.735.3702
Fax: 303.735.5185
FWA: 00003492

APPROVAL

14-Jan-2016

Dear Sally Wadsworth,
On **14-Jan-2016** the IRB reviewed the following protocol:

Type of Submission:	Amendment
Review Category:	Expedited
Title:	Colorado Adoption Project/Twin Study of Lifespan behavioral development & cognitive aging [CATSLife]
Investigator:	Wadsworth,Sally
Protocol #:	14-0421
Funding:	Federal
Documents Approved:	CATSLIFE Phenx Interview (14Jan16); 14-0421 Protocol (14Jan16); response to modifications required for 14-0421 1-12-16.docx; CATSLife Whole Questionnaire (14Jan16);
Documents Reviewed:	HRP-213: FORM - Amendment;
Description:	- Update for use of data from prior existing studies. - Submission of updated data collection instruments.
Notes:	- Information regarding duplicate versions of the Phenx Interview was removed from the Protocol. Only the currently submitted version of that instrument is included in the Approved Documents.

The IRB approved the protocol from **14-Jan-2016** to **07-Jul-2016** inclusive.

Before **7-Jun-2016**, you are to submit a completed FORM: Continuing Review (HRP-212) and required attachments to request continuing approval or closure. This protocol will expire if continuing review approval is not granted before **07-Jul-2016**.

Click the link to find the approved documents for this protocol: Approved Documents. Use copies of these documents to conduct your research.

In conducting this protocol you must follow the requirements listed in the INVESTIGATOR MANUAL

(HRP-103).

Sincerely,
Douglas Grafel
IRB Admin Review Coordinator
Institutional Review Board

University of Colorado Boulder

TITLE: Colorado Adoption Project/Twin Study of Lifespan behavioral development & cognitive aging [CATSLife]

PROTOCOL VERSION DATE: 12 January 2016

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PRINCIPAL INVESTIGATOR (PI):
Name: Sally J. Wadsworth, Ph. D.
Address: Institute for Behavioral Genetics, CU-Boulder 80309-0447
Telephone: 303-492-7362
Email: sally.wadsworth@colorado.edu

KEY PERSONNEL

Name: John DeFries, Ph.D.
Role in project: Co-Investigator

Name: John Hewitt, Ph.D.
Role in project: Co-Investigator

Name: Naomi Friedman, Ph.D.
Role in project: Co-Investigator

Name: Andrew Smolen, Ph.D.
Role in project: Co-Investigator

Name: Michael Stallings, Ph.D.
Role in project: Co-Investigator

Name: Soo Rhee, Ph.D.
Role in project: Co-Investigator

Name: Christian Hopfer, M.D.
Role in project: Co-Investigator for Pilot Study

Name: Sally Ann Rhea, B.S.
Role in project: Study Coordinator

Name: Corinne Gunn, B.A.
Role in project: Asst. Data Collection Coordinator

Name: Amy Ledbetter, B.A.
Role in project: Asst. IRB Coordinator

7/19/16
* questionnaire not attached but on file in research office.

Up to 20 undergraduate, 15 graduate, and 15 post-doctoral students may conduct analyses using study data. Up to five additional PRAs may assist the Study Coordinator by contacting subjects, scheduling interviews, processing consent and payment forms, tracking address contact information changes, and uploading data. All of the students and PRAs will have completed the CITI (continued updating is tracked by the Study Coordinator and/or one of the key personnel) and are directly supervised by one of the key personnel.

I. OBJECTIVES

Our overarching goal is to evaluate the unique saliency of early childhood factors to adult cognitive maintenance and change versus innovations (genetic and environmental) that emerge across development. The specific aims are:

1. Establish as an international resource the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife) at the cusp of middle adulthood. With prospective, genetically informative data collected almost yearly from birth to young adulthood CATSLife will become the first and only prospective study of genetic and environmental influences on behavioral development and cognitive changes.

2. Map individual differences in growth and maintenance of cognitive abilities approaching midlife. We propose that cognitive growth patterns--particularly in infancy/early childhood and adolescence when hippocampal and frontal cortex regions experience swift growth--will predict differential performance by midlife.

3. Evaluate physical factors and health behaviors associated with sustaining cognitive performance. There is ample evidence for relationships between midlife BMI, physical activity and functioning, and late-life cognitive health but little information about childhood/adolescence versus adulthood influences.

3a. Conduct a small pilot study to improve the detection of biomarkers associated with marijuana consumption. The reviewers of the original proposal specifically asked that we address substance use as a factor affecting cognitive resilience (Aim 3a). Marijuana particularly is important for this demographic and its biological substrate is poorly understood.

4. Trace biochemical and genetic pathways important to sustaining cognitive performance. We predict *APOE* and relevant gene pathways will strengthen in association with cognitive growth and maintenance.

5. Track environmental factors that decrease, sustain or boost cognitive performance as participants approach midlife. Cognitive, physical and social engagement in midlife may impact cognitive change but the nature and timing of these associations are unclear. We predict gene-environment correlations will contribute to these associations and strengthen in impact with age.

II. BACKGROUND AND SIGNIFICANCE

As the population ages, concerns about cognitive decline have become commonplace. According to the Centers for Disease Control, loss of mental capacity is feared two-fold over that of diminished physical ability, and over 60% of adults (18+ years) report worries about memory loss in late life. While there is substantial variation in the timing and magnitude of cognitive decline, little is known about their developmental genetic and environmental etiologies. If indeed "cognitive health begins at conception"[1], it implies that early influences accumulate over the life course to impact how well we age. Moreover, cognitive development during infancy, early childhood and adolescence, coupled with health and activity patterns, may lay down crucial cognitive reserves that hold a unique saliency to later cognitive functioning. A greater developmental understanding of the environmental (both social and physical) and genetic factors that drive increasing divergence in cognitive maintenance is fundamental to developing salient intervention points. Establishing a prospective study of genetic and environmental influences on

behavioral development and cognitive aging, as embodied in this protocol, addresses calls to evaluate individual differences in cognitive performance and change from a life course perspective.

This protocol will follow-up 776 Colorado Adoption Project (CAP) and 824 Longitudinal Twin Study (LTS) participants, now in their late 20's to mid- 30's, and enable us to address for the first time the developmental genetic and environmental etiologies that underlie individual differences in rates of age-related cognitive change, and apply both phenotypic and behavior genetic methods to data collected from infancy through early adulthood.

The significance of the pilot project is that it has the potential to advance the search for the etiology of marijuana dependence, which is currently hampered by the limited availability of biomarkers. Despite claims of the harmlessness of marijuana, scientific studies support the view that weekly use is associated with cognitive decline. In particular, it has been associated with an eight-point drop in intelligence in those who develop early-onset persistent dependence; importantly, the loss of cognitive capacity may not recover completely after desisting from marijuana use[2]. However, many previous studies on the effects of marijuana use are limited by lack of control of third variables or confounders that may influence both marijuana use and a drop in cognitive abilities; lack of assessment of premorbid functioning; and the difficulty of distinguishing the effects of marijuana from those of other substances or comorbid psychiatric disorders. For example, an alternative hypothesis explaining the association between marijuana use and cognition is that marijuana use is associated with the adoption of an unconventional lifestyle characterized by affiliations with substance using peers. Also, Lyons et al.'s[3] discordant twin study demonstrated no effect of regular marijuana use on cognitive function, a conclusion differing from many other studies. It is important to study the association between marijuana use and possible cognitive decline using a discordant twin design that can better disentangle causal pathways. Biomarkers may further elucidate pathways involved in cognitive decline.

[1]*Barnett JH, Hachinski V, Blackwell AD. Cognitive health begins at conception: addressing dementia as a lifelong and preventable condition. BMC Med 2013;11:246.*
[2]*Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(40):E2657-64.*
[3]*Lyons MJ, Bar JL, Panizzon MS, Toomey R, Eisen S, Xian H, et al. Neuropsychological consequences of regular marijuana use: a twin study. Psychological medicine. 2004;34(7):1239-50.*

III. PRELIMINARY STUDIES

Two years of ARRA funding were awarded in 2009 to initiate early adulthood assessment of 273 CAP participants at about age 30, including 114 adoptive probands; 20 unrelated siblings; 112 nonadoptive control probands; and 27 full siblings. [IRB protocol 0324.97]

IV. RESEARCH STUDY DESIGN

In order to reach a fuller understanding of the phenotypic, genetic and environmental underpinnings of factors that combine and interact to affect cognition and health across the lifespan we propose to test all available CAP probands and siblings and LTS twin pairs. We will focus upon physical health and cognitive function and examine the relations among traits within and between these domains, and intrinsic and extrinsic mediators and moderators, within early adulthood and across development. Based on our exceptional re-participation rate (nearly 90% for the CAP and 85% for the LTS) we expect assessments of approximately 1600 individuals, including 357 probands and siblings in adoptive families

and 419 probands and siblings in nonadoptive control families tested, as well as 824 twins. At the new assessment participants will usually be 28-38 years old (although there is no limit on the upper age). We anticipate collecting data across a six-year period but continuing to analyze it indefinitely. Current data may be analyzed in conjunction with all the data collected previously form these subjects (refer to attached tables for information on specific measures and ages). Previously collected data may also be analyzed independently as the entire data set contributes to an understanding of the objectives of this study. These data were originally collected under a variety of protocols dating back as far as 1975 (before protocols were numbered) that were later subsumed in 0324.97. These data were collected and are stored in the manner described below in data management section. All subjects were aware that they were participating in longitudinal studies.

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State-of-the-art analyses will be used to test hypotheses about longitudinal as well as age-specific multivariate phenotypic associations. Our ability to conduct joint analyses of data from twins, non-twin siblings, and adoptive siblings, as well as parents facilitates the investigation of more complex genetic and environmental influences not possible with each of these designs alone. Moreover, we use full information maximum-likelihood approaches to make use of all data, thus reducing bias due to attrition. The most relevant analytic approaches that we will use to address our most salient hypotheses are:

1. Structural Equation Modeling (SEM) has long been used in the CAP and LTS to address developmental issues central to our research and will be used to assess multivariate relations within and among measures of physical activity and cognitive function in early adulthood.

2. Cross-lagged models will be used to infer causal relations or reciprocal effects across traits, e.g., physical and cognitive functioning, or activities and cognitive.

3. Latent Variable Growth Curve Modeling will be employed to analyze development because it permits the modeling of change over age. Latent growth curve models (LGC) can be used with genetically informative data. In such applications, genetic and environmental contributions to individual differences in growth can be estimated.

4. Interrelationships between trajectories will be evaluated using multivariate dynamic models to examine cross-trait changes in physical health and cognitive traits across development.

5. Analysis of Measured Biomarkers and Genotypes will be conducted. Lipid and biomarker assays will be performed using established protocols. Fasting total cholesterol, HDL, non-HDL cholesterol, triglycerides and a calculated LDL will be assayed. Genomic DNA will be isolated from one ml of anti-coagulated blood samples. The genotyping array will include functionally-relevant variants in exonic (coding) or promoter regions as well as variants identified through genome-wide association (GWA) studies Additional variants unavailable on the commercial chips will be custom genotyped (i.e., 2 *APOE* SNPs).

6. Serum biomarkers and genotypes will be included as predictors in the models described above.

7. Analysis of Measured Environments to investigate mediation or moderation of the relationship between physical health and cognitive functioning. In addition, to various questionnaires, we will use geographic information systems (GIS) to obtain detailed information, including environmental profiles (e.g. distance to trails, parks, recreation centers) of subjects' current and previous neighborhoods.

8. Analysis of twin and adoptive siblings, and parents: plans and caveats. Apart from the pathway approach used to test for gene-sets in hypothesized pathways, we will apply the latest techniques in addressing type I error rates including false discovery methods. We will conduct pooled analyses of LTS and CAP longitudinal data which overlap in measures strategically, as well as parent and offspring at assessments with isomorphic data (16, 21, and 28-38). Measurement invariance will be evaluated across generations and time. We will evaluate the extent to which there is consistency of model fit and effect sizes within the CAP and LTS samples. Moreover, we have a singular advantage to compare within a single project the consistency of genetic variance estimates across designs. Last, the CAP and LTS studies

were begun approximately 10 years apart; however, the birth years of the CAP study overlap that of the LTS and we will evaluate cohort effects as a moderator of key findings.

The current proposal will test 1600 individuals from the child generation of CAP and LTS. Power analyses for univariate analysis of newly collected measures were conducted using the Mx statistical package. Conservatively, we used the average number of pairs tested to provide an approximate sample size available at any given assessment -- 210 MZ pairs, 185 DZ pairs, 100 non-twin sibling pairs, and 100 adoptive sibling pairs-- and computed typical sibling correlations for full-scale IQ. The average MZ correlation was 0.8; the average DZ correlation was 0.55; the average non-twin sibling correlation was 0.3; and the average adoptive sibling correlation was 0.05. "True" heritabilities were simulated ranging from 10% to 50%. Since adoptive pairs provide a direct estimate of shared environmental effects this was simulated at 5%. For heritabilities of 30% or greater, typical of cognitive and behavioral measures, power to reject the null hypothesis (heritability = zero) exceeded 94%. Tests of shared environmental influences were similar.

Use of multivariate designs, such as those of the CAP and LTS, have the beneficial effect of increasing statistical power over simple univariate analyses. However, power will vary depending on the phenotype of interest and how it is assessed (e.g., quantitatively or as a categorical trajectory class), the distributional properties or prevalence of the measured phenotype(s), the effect size(s), and the prevalence, distributional properties and effect sizes of potential moderating factor(s). For our proposed multivariate analyses, we assumed the same sample sizes as above, and considered a bivariate analysis with two measures (or the same measure at two assessment waves) having equal heritabilities ranging from 20% to 50%. To evaluate the power to detect a genetic correlation, we fixed environmental correlations at zero and varied the genetic correlation from 0.9 (not unusual among cognitive tests) to 0.1. For moderate heritabilities (30% to 50%), power was greater than 80% for detecting genetic correlations, even as low as 0.25.

In addition to the work being done at IBG, data analyses will be conducted at the University of California-Riverside and the Institute of Psychiatry, London. These institutions will be involved in data analyses only. They will not have any access to identifying information. Therefore it is possible that both IRBs will not regard their engagement as human subjects research but both are submitting the study for determination of status and review.

V. FUNDING

This primary project is funded by the National Institute on Aging (NIA 1RO1AG046938) and the pilot project is funded from Departmental funds from the CU-Denver Medical School.

VI. ABOUT THE SUBJECTS

No individuals who have not previously participated in our longitudinal studies are being recruited into the study.

The families in the CAP sample were enrolled from 1976 through 1983. The adoption portion of the sample was recruited through area adoption agencies. Pregnant women who intended to relinquish their children were invited by social workers to participate in a 3-hour assessment. Subsequent to their children's final placement, the adopting parents were invited to participate in the same assessments as well as annual home, laboratory, or telephone sessions for their children. A matched sample of parents giving birth to and rearing their children was recruited through area hospitals. The families in the LTS

were recruited with the assistance of the Colorado Department of Health (CDH) from 1984 through 1990, and, like the CAP sample, have been tested annually since birth.
For this protocol, all participants are age 28 and older with approximate equal gender distribution. Due to the circumstances of initial recruitment, the sample is primarily non-Hispanic Caucasian (90% for the CAP and 85% for the LTS). The inclusion criterion is being a member of one of these two samples. We anticipate that almost all of the subjects will choose to participate.
The subjects are divided into two pools: the primary pool and a second pool comprised of the portion of the LTS sample who are also participating in protocol 11-0614 (an fMRI study).
Fifteen twin pairs will be recruited into the pilot study. Ten will be concordant for recent marijuana use and five will be discordant.

Subject Population(s)	*Number to be enrolled in each group*
Members of IBG's adoption and twin longitudinal studies	*1600*

VII. RECRUITMENT METHODS

Subjects are drawn exclusively from the samples of past participants in the CAP and LTS. They will be contacted, according to their previously stated preferences, by telephone, text, e-mail, post mail, or Facebook and invited to learn more about the study through one of those methods. If they agree to participate, they will be sent, again by their preferred method, a link to a website and unique "token" to enter the site and enroll.
We will offer twin pairs the opportunity to participate in the pilot study if they are able to schedule their sessions at about the same time and their in-person sessions on a weekday.

List recruitment methods/materials and attach a copy of each in eRA

1. *CATSLife Sample recruitment script*
2. *Pilot recruitment script*

VIII. COMPENSATION

Payment for completion of all the procedures will be $200 (or $250 if pilot study participant) which usually will be paid in cash at the conclusion of the in-person session. For partial completion, compensation for the types of data collection (see procedures below) will be paid as follows:
Primary pool
On-line--$30
In-person--$100
Blood draw--$20

Second pool
On-line--$15
Telephone interview--$15
In-person--$100
Blood draw--$20
Pilot Study blood draw and urine sample--$50 (for 30 individuals; this additional payment is primarily compensation for scheduling together and on a weekday)

In effect there is a $50 bonus for completing all segments of the data collection.

Subjects will also receive reimbursement for their travel costs, locally at the current CU-Boulder mileage rate and distantly at the state authorized travel rates. In the rare case in which a subject pays for the blood draw we will reimburse them for that cost.

IX. CONSENT PROCESS

Subjects will consent on-line on a secure site. These participants have completed consent forms in this manner multiple times. Upon "signing" the consent with the last four digits of their SSN, they will obtain access to the on-line forms. Appointments for the phone interview and in-person session will have been made during the communication that led to on-line access. At the beginning of the phone call, the interviewer will remind the participant about the types of questions he or she has consented to answer as well as about his or her right to skip any question or stop participating. A copy of the "signed" consent will be reviewed before the in-person session begins and the subject will be asked to initial and re-date the form to indicate continued understanding of the procedures and agreement to participate.

X. PROCEDURES

Depending on the sample pool there are three or four types of data collection:
1. On-line questionnaire assessments
2. Telephone interviews (second pool only)
3. In-person cognitive and for first pool psychological assessments
4. In-person physical assessments, including blood sample collection

After "signing" the on-line consent, both pools will have immediate access to the on-line portion of the study which is a questionnaire that will be very familiar in style and content to questionnaires they have completed before with questions and check boxes to click and enter answers. They will be able to complete the questionnaire in one sitting or return to it later at their convenience. Specific assessments are described in the data tables below.

If they are pool two participants, an interviewer will call them at a time scheduled during the recruitment call to conduct an interview. After reviewing the consent, the research assistant will ask a series of questions with branching sets depending on the responses. Specific assessments are described in the data tables below.

In most cases subjects will travel to our lab for a day of testing on cognitive, psychological and physical assessments. If they are unable to visit us, we will travel to their location and make arrangements to conduct the tests in another private space such as a fellow institution, a reserved library conference room, or a conference room in a hotel. Due to the blood draw, subjects will be scheduled in the morning because an 8-hour fast prior to collection is required. Juice and snacks will be provided subsequent to the blood draw. The physical assessments will be conducted first and consist of various measurements as described below. The blood sample will be drawn at one of Clinical and Translational Research Center (CTRC), Boulder Community Hospital (BCH), the participant's physician's office or lab. The standard location is the CTRC, but because the facility is not open most weekends, many subjects assessed on the weekends will have the draw done at BCH. In either case a member of the study team will meet the subject at the facility, provide the facility with a bar coded label for the collection tube, and will take receipt of the tube to transport it to the IBG storage facility. IBG will have accounts set up in both locations to pay for the draw. If we travel to the subject's location, we will ask him or her to arrange a private collection of the sample prior to the visit. If the participant agrees we will mail her or him a collection kit with a reply mailer and will provide reimbursement for the cost. Upon receipt these samples will be placed in the IBG storage facility. An additional blood sample and a urine sample for the

Pilot Study will be collected at the CTRC (limiting participation to those who can be tested in Boulder and on a weekday).

Most of the cognitive assessments (see data table and descriptions below) are follow-ups to those they and their parents have completed in the past. The first is a specific cognitive abilities battery (Hawaii Family Study of Cognition; HFSC) which is a compilation of assessment from various sources and has been used extensively in projects at IBG and elsewhere. The second is the internationally standardized Wechsler Adult Intelligence Scale-III (WAIS-III). Finally a test of executive cognitive function will be administered; this is a follow-up for the LTS sample but a new test for the CAP participants.

The questionnaire assessments listed below by domains have been submitted to the IRB both individually in their source form and (for the most part) in an omnibus form in the order (counter-balancing types of questions to reduce response bias and fatigue) and format experienced by the subjects. The ICU, administered only to Protocol Two subjects, is not included in the omnibus version. It should be noted that the omnibus is a pdf of the computer-generated questionnaire: the subject sees the questions in small sets and many items are skipped depending on answers to stem questions. Additionally, in a few cases particular items have been dropped or slightly reworded to modern terminology in the omnibus version.

We have also provided two versions of the substance use interview—one in the original PhenX format and one in our Lime Survey format. By license agreement no modifications of any kind are allowed for the DIS so only one version of that instrument is needed.

Protocol One

Type	Instrument	Purpose	Duration
On-line	CAP Health History Q; AddHealth health questions; Sleep quality questionnaire;	Self-report of health and medical history	1 hours, 30 min
	PhenX food diary and caffeine consumption	Self-report of food preferences	
	CAP religion	Self-report of religious involvement	
	CAP activity Q	Self-report of activities	
	PhenX Toolkit leisure & physical activity	Self-report of activities	
	NNSD Neighborhood demographics		
	EASI temperament survey; Big Five Inventory of personality	Personality assessments-*Multiple assessments are needed for both isomorphic comparisons with parents and self from past sessions and to meet current standards*	
	Mood and Anxiety Symptom questionnaire; Barrat Impulsiveness Scale; Adult Self-Report Scale of ADHD (Attention Deficit Hyperactivity Disorder; Behavioral Risk Questionnaire regarding high-risk sexual practices,	Standard questionnaire assessments of psychiatric problems	
	Penn State Worry Questionnaire; Ruminative Responses Scale;	Standard questionnaire assessments of adult rumination	
	Educational and Occupational Attainment (NNSD)	Self-report of educational & occupational accomplishments and goals	
	Dyadic Adjustment Scale; Family quality; Close relationship quality, Social support; AddHealth marital status, number of children, number of friends	Standard questionnaire assessments of family and friend relationship status and quality	
	Life Events; Satisfaction with Life Scale; Ryff psychological well-being; Financial well-being	Life events and standard questionnaire assessments of life events stressors and emotional well-being	
In-person Psychology & Substance Use*	DIS Anxiety, Depression, and Antisocial Personality	Standard interview assessing psychiatric problems	30 min
	PhenX Toolkit Substance Use	Standard interview assessing substance involvement	
In-person Cognitive	Subset of Hawaii Family Study of Cognition (highest loading)	Assessment of specific cognitive abilities [previously administered to subjects and their parents	3 hours, 30 min
	Wechsler Adult Intelligence Scale III	Standard assessment of cognitive abilities	
	Antisacccade, Stroop (inhibition); Keep Track, Letter Memory (updating); Category Switch, Letter/Number (shifting)	Computerized tests of executive cognitive abilities	
In-person Physical & Geocode	24-hour report on exercise, caffeine, eating, and sleep; Safety questionnaire	Standard questionnaires of recent health activity and safety screen for measures	45 min
	Height, weight, waist and hip circumference	Body size/ratios (BMI) as a measure of health	
	Handgrip strength, resting blood pressure, resting heart rate, forced vital capacity; Geocode	Physical functioning & neighborhood characteristics as a measure of health	
	Blood draw	Lipid (e.g. cholesterol) and DNA (e.g. APOE) assessments	
Total time			**~ 6 hours**

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Protocol Two (for LTS subjects who are also participants in fMRI study 11-0614)

Type	Instrument	Purpose	Duration
On-line	CAP Health History Q; AddHealth health questions; Sleep quality questionnaire;	Self-report of health and medical history	1 hour, 30 minutes
	PhenX food diary and caffeine consumption	Self-report of food consumed	
	CAP religion	Self-report of religious involvement	
	CAP activity Q	Self-report of activities	
	PhenX Toolkit leisure & physical activity	Self-report of activities	
	NNSD Neighborhood demographics		
	EASI temperament survey; Big Five Inventory of personality	Personality assessments-*Multiple assessments are needed for both isomorphic comparisons with parents and self from past sessions and to meet current standards*	
	Mood and Anxiety Symptom questionnaire; Barrat Impulsiveness Scale; Adult Self-Report Scale of ADHD (Attention Deficit Hyperactivity Disorder); Behavioral Risk Questionnaire regarding high-risk sexual practices; Inventory of Callous and Unemotional Traits	Standard questionnaire assessments of psychiatric problems	
	Penn State Worry Questionnaire; Ruminative Responses Scale; Ruminative Reflection Questionnaire, Rumination subscale	Standard questionnaire assessments of adult rumination	
	Educational and Occupational Attainment (NNSD)	Self-report of educational & occupational accomplishments and goals	
	Dyadic Adjustment Scale; Family quality; Close relationship quality; Social support; AddHealth marital status, number of children, number of friends	Standard questionnaire assessments of family and friend relationship status and quality	
	Life Events; Satisfaction with Life Scale; Ryff psychological well-being; Financial well-being	Life events and standard questionnaire assessments of life events stressors emotional well-being	
Telephone Interview	DIS Anxiety, Depression, and Antisocial Personality	Standard interview assessing psychiatric problems	45 minutes
	PhenX Toolkit Substance Use	Standard interview assessing substance involvement	
In-person Cognitive	Subset of Hawaii Family Study of Cognition (highest loading)	Assessment of specific cognitive abilities [previously administered to subjects and their parents	2 hours
	Wechsler Adult Intelligence Scale III	Standard assessment of cognitive abilities	
In-person Physical & Geocode	24-hour report on exercise, caffeine, eating ,and sleep; Safety questionnaire	Standard questionnaires of recent health activity; safety screen	45 min
	Height, weight, waist and hip circumference	Body size/ratios (BMI) as a measure of health	
	Handgrip strength, resting blood pressure, resting heart rate, forced vital capacity; Geocode	Physical functioning & neighborhood characteristics as a measure of health	
	Blood draw (and for 30 pilot subjects urine sample)	Lipid (e.g. cholesterol), DNA (e.g. APOE) assessments & pilot marijuana markers	
Total time			**~ 5 hours**

*Subjects may request to participate in this segment of the in-person session via a phone interview instead.

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The following are descriptions for measurements for which hard copies cannot be uploaded due to either proprietary rules or the nature of the task.

Wechsler Adult Intelligence Scale-III

Various Wechsler tests of intelligence are internationally normed measures and the standard for cognitive assessment. The test consists of verbal tasks, such as vocabulary, and performance tasks, such as assembling puzzles. Even though there is a more current version, we are using this edition because it is isomorphic with the participants' own past assessments and closer to the assessment given to their parents than is the current edition [Wechsler D. *Manual for the Wechsler Adult Intelligence Scale–3rd Edition*. San Antonio, TX: The Psychological Corporation; 1993.]

Computerized test of executive cognitive abilities

Inhibiting. On each trial of the antisaccade task, a small visual cue briefly flashed on one side of the computer screen for 200 ms, followed by a target (a box containing a number) that appears for 150 ms before being masked. To see the target for long enough to identify the number, participants have to inhibit the automatic tendency to saccade to the cue and instead immediately saccade in the opposite direction. The dependent measure will be the proportion of correctly identified targets. In the Stroop task, participants name the font colors of incongruent color words (e.g., say "blue" when presented with the word RED printed in blue), congruent color words, and strings of asterisks matched in length to the words. Hence, on incongruent trials they have to resist the dominant tendency to read the words. The dependent measures will be the difference between the average response times for the incongruent trials compared to those for asterisks or congruent trials.

Updating. In the keep track task, participants are given 2 to 5 target categories (e.g., animals and countries). After viewing a serial list of 15-20 words drawn from 6 categories, they have to recall the last exemplar of each target category. Because each list contains 2-3 exemplars of each category, they have to update which exemplars to remember during the lists. The dependent measure will be the proportion of the words correctly recalled out of all trials. In the letter memory task, participants see series of letters appear on the screen. For each letter, they must report the last 4 letters. Hence, as each new letter appears, the participant must update which letters to report, dropping the 5th one back and adding the new letter. The dependent measure is proportion of letter sets reported perfectly.

Shifting. In the category switch task, participants see words presented with symbols classifying the object as living or nonliving or as bigger or smaller than a soccer ball. Participants complete blocks in which they only have to do one type of categorization as well as blocks in which they have to switch in an unpredictable sequence (via random cues) between the two types of categorization. The dependent measure will be the shift cost, calculated as the difference between the average RTs of the target trials that require a mental and the average RTs of the trials that require no mental shift. The number-letter task is set up similarly, except the stimuli are number-letter pairs (e.g., 4A), and the participant has to categorize the number as odd/even or the letter as consonant/vowel, depending on the location of the stimuli on the screen.

Physical assessments

The blood draw will be collected at a professional clinic or by Interviewers who have completed phlebotomy training will collect the blood sample. Subjects' weight and height will be measured on a standard balance scale. They will hold a tape measure at their waist and hip line and turn slowly to wind the tape around their bodies; the interviewer will record the measurement but will not need to touch the subject to take these measurements. Blood pressure and resting heart rate will be taken 3 times: once after subject has been sitting quietly for 5 minutes, then at 1 minute intervals thereafter.

Two assessments of lung health will be performed by measuring forced vital capacity (FVC), which is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration, and the forced expiratory volume (FEV) in one second. Hand grip strength will be measured using a standard procedure in which the subject grips a bar in each of the left and right hand as hard as

he or she can; we will conduct three trials on each hand at 20 sec intervals and record dominant handedness.

XI. SPECIMEN MANAGEMENT

Blood samples will be delivered daily and stored in IBG's DNA laboratory. Annual shipments of stored whole blood samples will be delivered directly by a member of the study team to iC42, Clinical Research & Development, a Service Center at the University of Colorado Denver. iC42 is headed by Uwe Christians, PhD of CU Denver. Dr. Christians has noted expertise on biomarkers, including proteomics and biochemical profiling. Lipid biomarkers and BDNF biomarker assessments will be performed using established procedures. The iC42 labs are experienced in performing lipid panels and brain derived neurotrophic factor (BDNF) assays. Lipid markers to be assayed include (fasting): Total Cholesterol, HDL, Non HDL Cholesterol, Triglycerides and a calculated LDL. BDNF assays will be performed using standard Elisa kits. DNA isolation and quantification (by PicoGreen fluorescence) will consist of one genome-wide SNP panel for each sample but focus on three targeted SNPs in BDNF and APOE genes.

The blood and urine samples collected from twins either discordant or concordant for past 30 day marijuana use will be shipped by the CTRC directly to Proteomics Core Lab facility at the University of Colorado at Denver Once a final sample of 10 discordant and 5 concordant pairs is available, the blood serum will be analyzed and the frozen buffy coat samples will continued to be stored at the Proteomics Core Lab facility. Urine THC concentrations will provide a standard biomarker comparison to protein expression levels in the blood samples. The urine sample will be used to measure THC (the active ingredient in marijuana) and other drug metabolites. Lymphocytes will be stored for potential future studies examining epigenetic changes, such as whole genome methylation, associated with marijuana use as well as correlating these with proteomic markers. Epigenetic studies are currently entirely for research purposes only and we do not anticipate any potential incidental findings. The UC Denver lab will not have access to any identifiers.

XII. DATA MANAGEMENT

Interviewers are assigned a specific subject to interview. All test materials for that subject will be labeled with a bar-coded identification number. Upon completion of the test, the interviewer will return the consent form with the subject's name and the bar-coded paper-and-pencil test materials (HFSC and WAIS-III) to the Study Coordinator or one of the lead assistants. Identifying materials (consents) are separated and stored in a locked filing cabinet. Materials labeled with subject ID are filed in locked cabinets in a different location.

The address history form contains identifiable information—the addresses themselves. Therefore the form will be stored with the consent form after the addresses have been recoded to retain only census tract data. The latter will be stored with other paper data.

For the online data collection, we use an industry standard SSL connection. This safeguards information in transit between the subject's computer and the study's server. Once a subject has completed an online questionnaire the data is no longer viewable except to authorized study personnel, so even poor password management on the subject's part will not expose any information.

No sensitive data will be collected on laptop computers. EF cognitive tasks will be collected on laptops but the results are in code that is meaningless before being transformed by software at the analyses stage subsequent to uploading onto secure servers

We have in place a simple barcoding system for tracking of data. Each subject is assigned a unique numerical ID. A set of barcode labels for that ID are produced and these are placed on collection tubes

as well as on the paper test materials. The barcodes then "follow" all materials related to the subject during phenotype and DNA collection. When field testers collect the blood it is delivered to IBG's DNA facility and the bar code is scanned to identify the sample prior to long-term storage in -80C freezers. In this way, samples, subject IDs and phenotypic data share common physical labels and there is almost no opportunity for sample mix-ups to occur. The bar coding system has been in place for many years and has eliminated typographical errors frequently associated with large sample numbers. The personnel who process the blood samples do not have access to subjects' identities or phenotypic data and therefore all samples are held essentially anonymously.

The data from the Pilot Study blood and urine collection will be analyzed by Dr. Christian Hopfer, but he will not have access to any identifying information about the subjects.

Access to the data archive is only available to authorized users who must validate themselves to the computer system before being allowed data access. The computers used to store study data are actively managed by IBG personnel to insure that the systems are secure and conform to the University of Colorado's information security policies and all personnel are required to take on-line training in Information Security Responsibilities.

Thus, the DNA and genetic data are held in the highest confidentiality as physical materials reside in locked storage and all links between subjects' actual identities and subjects' numerical IDs and between subjects' numerical IDs and the phenotypic and genotypic data sets are maintained in separate systems. Only high level authorized personnel have access to either system and no-one has access to both systems.

To further protect confidentiality, we applied for and received a Federal Certificate of Confidentiality which protects scientific data from subpoena or criminal justice investigation.

Due to the longitudinal nature of the study we do not foresee destroying the data or the identifying links. However, participants may ask to have their data removed from any further studies by notifying the research team in writing. If the unforeseeable occurs, the system containing identifying links will be purged.

XIII. WITHDRAWAL OF PARTICIPANTS

The subjects who will be invited to participate in this project have participated in related projects many times before and are unlikely to withdraw now although some may chose not to complete specific portions of the study. There is no circumstance under which we would withdraw subjects though we may postpone data collection if the subject does not seem capable of meaningful consent and participation. Because all subjects must be part participants there is no way to replace subjects if any withdraw.

XIV. RISKS TO PARTICIPANTS

The risks associated with completing these assessments are not greater than those encountered during the performance of routine medical examinations or tests. There is a small chance that subjects will become distressed or embarrassed about some interview items. There is a small medical risk associated with venipuncture including pain and possible brief lightheadedness or nausea. The primary potential risk is a break in confidentiality.

XV. MANAGEMENT OF RISKS

If subjects appear to experience distress, the researchers are prepared to make referrals to local mental health agencies. We intend to offer juice and snacks immediately after collecting the blood sample. Protection from the risk of a breach in confidentiality is described in the Data Management section..

XVI. POTENTIAL BENEFITS

There are no direct benefits to subjects.
The knowledge to be gained is important because the adoption design provides the cleanest possible separation of the combined inherited biological and family environmental influences, end the study of collateral pairs of twins and siblings provides unique information concerning both the timing and character of the total range of biological and environmental factors acting throughout the developmental process. Data from an adoption and twin design that includes longitudinal assessments of the children's development and their home environments will greatly facilitate analyses of the etiologies of change and continuity in development through the lifespan. Just as phenotypes can change with age, gene expression and the influence of the environment can change with age. Despite the recognized strengths of the adoption/twin design, there have been relatively few adoption studies of behavioral development within the normal range on related and unrelated sibling pairs and their parents, and none, to our knowledge, with parallel data from a large number of twin pairs and their parents.

XVII. PROVISIONS TO MONITOR THE DATA FOR THE SAFETY OF PARTICIPANTS

The Study Coordinator will have primary responsibility for this monitoring and although systems are in places to prevent problems, will report to the PI any breaches in confidentiality, Adverse Events, and Serious Adverse Events. The PI will promptly inform the appropriate IRB and make any needed corrective actions.

XVIII. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

There are no risks to privacy interests other than a breach in confidentiality which is discussed in the data management section.

XIX. MEDICAL CARE AND COMPENSATION FOR INJURY

The research is not more than minimal risk.

XX. COST TO PARTICIPANTS

There is no cost to participants.

XXI. SHARING OF RESULTS WITH PARTICIPANTS

We do not plan to share results with participants.

Amendment CR 7/8/16

Updated 3.26.12

Original Approval exempt #4

UNIVERSITY OF CALIFORNIA RIVERSIDE
Human Research Review Board

REQUEST FOR AMENDMENT TO APPROVED PROTOCOL

This form must be typed and approved prior to implementation of requested changes. *Please do not staple any documents.* Submit form and required attachments to the UCR Office of Research Integrity, 210/211 University Office Building, Riverside CA 92521-0217. Please note, it might be helpful to write out the sections of this amendment in Microsoft Word or a similar program and conduct spell check before transferring over to the HRRB document. These steps might resolve complications of using spell-check within the soft copy of the HRRB amendment.

Principal Investigator: Chandra A. Reynolds	Email: chandra.reynolds@ucr.edu
Department: Psychology	Phone Number: 951-827-2430
Protocol #: HS 14-073	
Title of Original Study: Colorado Adoption/Twin Study of Lifespan behavioral development & cognitive aging (CATSLife)	

1. Provide a brief description of original protocol:

The primary project objective is to evaluate the unique saliency of early childhood factors to adult cognitive maintenance and change versus proximal influences and innovations that emerge across development. The aims are to: (1) conduct a genetically sensitive study of individual differences in behavioral and cognitive change at the cusp of middle adulthood, in 1600 participants studied almost yearly from birth to early adulthood; (2) map individual differences in growth and maintenance of cognitive abilities; (3) evaluate physical factors and health behaviors associated with sustaining cognitive performance; (4) trace biochemical markers and measured genetic pathways important to sustaining cognitive performance; and (5) track measured environmental factors that might decrease, sustain or boost cognitive performance.

The participant sample is already in place; the proposed research is a longitudinal follow-up of the existing sample of the Colorado Adoption Project (CAP) comprising adoptees, matched controls and their siblings, and twin pairs of the Longitudinal Twin Study (LTS), also based in Colorado. At time of funding the target participant sample is primarily between ages 30-40 years and includes those up to age 45. All participants are contacted and tested by personnel at the University of Colorado at Boulder, Institute for Behavioral Genetics (CU IBG).

The UCR protocol makes use of de-identified data provided CU IBG. The value of the longitudinal follow-up is that the de-identified data from the ongoing follow-up are analyzed with the archival data on these participants that exists from infancy.

There is wealth of knowledge to be gained by the follow-up of these participants as they approach midlife. Both early life and midlife health and activity patterns have been proposed to be pertinent to later life aging outcomes, including cognitive aging, but no existing samples apart from CATSLife have prospective data to consider these associations.

2. Describe the modification(s) requested, including the reasons for the change(s). Attach any new or revised paperwork.

APPROVED

The amendment clarifies that the UCR site will conduct data coding as well as data analysis of de-identified data provided by CU IBG. This includes conducting geocoding of de-identified data. The use of geographic information systems (GIS; geocoding) to measure environmental profiles was described in our funded NIA grant application, under Aim 5.

For geocoding, the CU IBG site will prepare a dataset(s) for the UCR site with randomly generated alternate ID's (tokens), latitude and longitude for each participant's address at each time of assessment, and year. The tokens will be generated for each address for each year and sorted to break up any potential patterns.

UCR will not have access to any files linking these alternate ID's to the main study ID; only CU IBG will retain a file linking the main study ID to the alternate ID's (tokens). UCR will send back the alternate ID's and geocoding output

variables at which point CU IBG will merge back the geocoding output variables to the main datasets and remove the alternate ID's (tokens). For example, we at UCR will be coding for distance to parks, walking/hiking trails, and recreations centers, features that may facilitate activity and exercise; we will identify parks, trails, recreation centers within a radius (or within a census block or tract). We will conduct an analysis to measure distances for each latitude and longitude sent to UCR with the latitude and longitude of parks, trails, etc., that we identify within the radius. Other summary variables of interest for each radius include demographic, socio-economic, and public health information of a particular radius (or within a census block or tract) such as population density, income distribution, gender and ethnic make-up, age distributions, home values, crime statistics, and public health (e.g., numbers of hospitals and healthcare facilities). The kinds of geographic software tools used to do geocoding will include SimplyMap, Social Explorer, and ArcGIS (including auxiliary resources such as demographic data and basemaps).

Measures to ensure non-identification of participants include:

- The de-identified data files provided to UCR will only include randomly generated alternate ID's (tokens), latitude and longitude for each participant's address at each time of assessment, and year.
- No additional participant data collected from prior waves or the current follow-up will be included in the files provided to UCR.
- The tokens generated for each address and year will be used to sort the records to break up any potential patterns (done at CU IBG before sending data files to UCR).
- The CU IBG site plans to insert some random latitude and longitudes not belonging to any participant, as an extra measure.
- Only the data collection site, CU IBG, will retain a file linking the main study ID to the alternate ID's (tokens).
- All files will be password protected with access limited to authorized project personnel engaged in the geographic information systems (GIS; geocoding) data management, coding or analysis.

3. In your opinion, will the modification(s) increase or decrease the risk of harm to participants?
   - ☒ Neither
   - ☐ Decrease
   - ☐ Increase. Please provide a justification for the proposed changes.

4. Will the modification(s) alter the approved consent form?
   - ☒ No
   - ☐ Yes. Attach (1) the original approved consent form, (2) *the revised consent form* with all changes highlighted, and (3) a clean copy of the revised consent form. Failure to do this may result in an increased review period.

Principal Investigator	**Faculty Advisor (if applicable)**
Chandra A. Reynolds Printed Name Chandra A. Reynolds 7-18-2016 Signature Date	Printed Name Signature Date
Department Chair/Director/Dean	**APPROVED: Institutional Review Board**
Printed Name Signature Date	M. Wicker Printed Name 7/19/16 Signature Date