Study Title:

Gas Exchange Kinetics and Work Load During Different Exercise Protocols in Healthy Children and Young Adults

Date:

January 26, 2018

UCI Office of Research

Institutional Review Board
Human Research Protections
Protocol Narrative ~ Expedited/Full Committee
Biomedical/Clinical Research
Version 2015

Upload this completed narrative and any supplemental documentation to the IRB Application.	**IRB USE ONLY –** **HS#: 2015-2467**
Lead Researcher Name: DAN M. COOPER, MD	
Study Title: GAS EXCHANGE KINETICS AND WORK LOAD DURING DIFFERENT EXERCISE PROTOCOLS IN HEALTHY CHILDREN AND YOUNG ADULTS	

CLINICAL TRIAL MASTER PROTOCOL AND INVESTIGATIONAL BROCHURE INFORMATION *

	Master Protocol	**Investigator Brochure:** <Specify Drug/Device>	**Investigator Brochure:** <Specify Drug/Device>	**Sponsor Consent Form Template(s)**
Version #:				
Version Date:				

[X] This study is investigator-authored (investigator developed the study and is conducting the study at UCI and/or with other non-UCI sites).

NON-TECHNICAL SUMMARY

Provide a brief non-technical summary or synopsis of the study that can be understood by IRB members with varied research backgrounds, including non-scientists and non-affiliated members.

The purpose of this research study is to understand how different kinds of exercise affect the human body and the health of the heart and lungs. For example, some people like to exercise continuously for relatively long periods of time while others like to exercise for short periods of time with rest periods in between. Children tend to exercise in frequent bouts of brief exercise interspersed with periods of rest. Also, some people like running or treadmill exercise while others like to work out on stationary bicycles. To date, standard exercise testing is based on a century-old paradigm used predominantly for adults that involves maximal exercise protocols (cardiopulmonary exercise testing–CPET). Moreover, different but widely used exercise modalities such as cycle ergometer and treadmills are currently impossible to compare in children, and this has limited the clinical and research application of such testing in the pediatric age-range. A major premise of our laboratory is that laboratory testing of cardiopulmonary fitness in children should be based on protocols that mimic naturally occurring patterns of exercise in children, rather than those that have been artificially employed to assess maximal efforts in adults. This research project designed to begin the process of systematically identifying protocols can be best used for children and young adults. Participants will exercise in different protocols on a bicycle ergometer or treadmill. This research could lead to improved and more

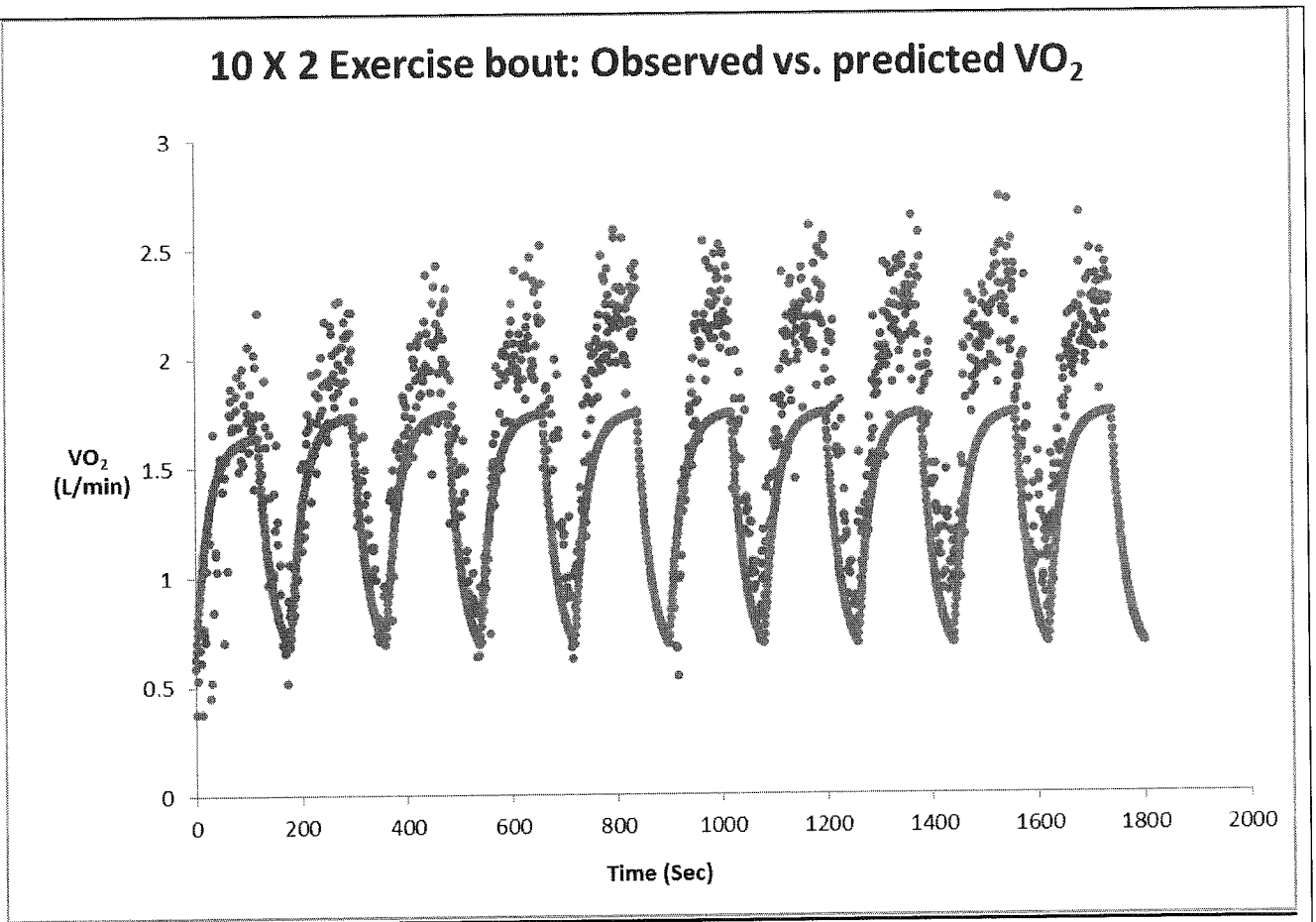
accurate fitness assessment and pave the way to an improved personalized exercise program in health and illness.

SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH

1. Provide the scientific or scholarly rationale for the research. Describe the relevant background information and the specific gaps in current knowledge that this study intends to address.

Children are naturally the most physically active human beings, and using exercise has long been viewed as a promising approach for disease diagnosis and therapy. However, exercise testing has not achieved its promise in either clinical application or translational science. One barrier has been in the kind of cardiopulmonary exercise testing (CPET) that is typically used in the pediatric population. Another major barrier has been that CPET in children is done with two different modalities: treadmill and cycle ergometer ("stationary bicycle"). The extent to which these two different types of CPET data are interoperable in children is not known.

Maximal oxygen uptake (VO2max or peak) is the current gold standard of CPET in both children and adults. Maximal exercise testing is based on century old concepts informed by the false assumption that physiological systems are integrated to perform maximal efforts. More recently, however, there is a growing body of literature to suggest that maximal exercise testing fails to identify impaired responses that are critical components for diagnosis and therapy in children. First, maximal exercise is rarely seen in natural physical activity. Second, maximal exercise testing depends in large measure on the ability of the child or adult to exercise in a range of activity that is perceived as uncomfortable; consequently, one's ability to reach maximal levels is highly dependent on cognitive choices and not necessarily on physiological determinants. The point of this research is to gather preliminary and pilot data that we will use to more formally test innovative noninvasive approaches to assessing fitness in children. We will explore several promising areas: 1) the ability of a child to rapidly increase the integrated physiological responses necessary to perform physical work; 2) the time required in the sudden transition from rest to exercise (mimicking the need, for example, to escape predation) and then to recover from the exercise; and 3) the interoperability of examining these responses using the two most common modalities of laboratory CPET, treadmill and cycle ergometer. We discovered many years ago that in order to successfully test a child's response to heavy exercise, we needed to use protocols that mimic the stop-start activity of natural physical activity. We developed an exercise protocol that uses ten, 2-min bouts of constant work rate exercise interspersed with 1-min rest. We never formally assessed the on- and off-transients of gas exchange or heart rate in these approved studies. Occasionally, the child did remain on the mouthpiece and we captured gas exchange and heart rate data. An intriguing example that has prompted this proposal is seen in the figure below. The actual oxygen uptake data (VO_2) are shown in red. We imposed a predicted response based on equations obtained in adults. Note that the adult predictive equations failed to fit the actual data obtained in the child. **It is clear that pilot and exploratory studies are needed if we are to transform this field and enhance the use of exercise testing in clinical and research child health care. No such pilot data exist that one could use to perform either power analyses or data precision calculations.**



Our study includes the following procedures and rationale:

- CPET – maximal ramp test was found to correlate with fitness in children and adults. Results of the ramp test would be used to configure the intensity and the exercise bouts protocol.
- Brief exercise protocol – exercise protocol that uses ten, 2-min bouts of constant work rate exercise interspersed with 1-min rest. (n.b., the CPET and "10x2" test will be done on both the treadmill and the cycle ergometer). The **rationale** for this is so we can compare the two types of exercise tests commonly used in children.
- Physical activity questionnaire and Godin Leisure Time Exercise questionnaire – physical activity by questionnaire was found to correlate to cardiopulmonary fitness assessments. By using these validated questionnaires we hope to find correlation to different fitness parameters and hence to use a simple and widely used tool for the pediatric population.
  Rationale: Questionnaires are commonly used to assess perceived difficulty. Comparing cycle ergometer to treadmill will be an important parameter in determining the interoperability of the two modalities.
- Growth and development questionnaire - Exercise through puberty is of great interest and significant changes are reported among boys and girls.
  Rationale: Interpreting data from children regarding physical activity depends on an assessment of the developmental stage of each child.
- Dual X-ray Absorbiometry (DXA) - Oxygen consumption highly correlates to lean body mass (as measured by DXA) and better differentiate body composition than total weight or body as index (BMI). In a study done in our lab, we found a very strong correlation between lean body mass and both peak VO2 and extrinsic, size-dependent CPET slopes. Each participant will undergo a DXA scan to determine body composition.
  Rationale: Exercise responses are determined in large measure by lean and fat tissue

distribution. Determining the interoperability of the two modalities will rest on how each is precisely influenced by lean and fat mass.

- Ultrasound - Recently, the importance of muscle mass (by magnetic resonance imaging, MRI) as a determinant of CPET biomarkers in adolescents was shown. In our study, each participant will be evaluated by ultrasound - non invasive muscle mass measurement shown to highly correlate with MRI (gold standard for muscle mass measurements).
- **Rationale:** Ultrasound provides specificity of muscle mass (i.e., particular groups) not available in DXA assessment.
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- Respiratory sensors– The importance of identifying different breathing patterns during rest and exercise can be useful in healthy population as well as in disease and chronic conditions. Breathing patterns (breath rate and volume) will be evaluated by a non-invasive ultrasensititve piezoresistive strain sensors capable of measuring large mechanical strains of the chest during breathing. The sensors have a form factor of a disposable BandAid© and will be worn on the upper torso during rest and exercise.

  Rationale: Spirometry measurements provide information on breath rate and lung volumes at a specific point in time while the respiratory sensors will provide **continues** breath rate and lung volume data during rest and exercise

Maximal exercise has been the gold standard for 100 years in children; however children with chronic disease are unable to achieve maximum levels, thus diminishing the role of maximal exercise in identifying biomarkers of health and disease. It becomes clear that progressive exercise testing, while suitable for gauging maximal work, is inadequate in attempting to quantify fitness levels in children with chronic diseases or disabilities.. Submaximal exercise testing protocols in which the magnitude and duration of the work rate is characterized by short intervals with varying degrees of difficulty and rest will be able to distinguish a difference among healthy subjects that a maximal cardiopulmonary exercise testing would not be able to predict.
This new approach will yield the data needed to develop a mathematical model characterizing the exercise kinetics in children and young adults.

2. Provide relevant preliminary data (animal and/or human).

The PI has been a pioneer in examining on and off transience recovery times as a function of growth and development in healthy children and children with chronic diseases. This laboratory has been responsible for seminal observation showing that kinetics of VO_2, heart rate (HR), and Carbone dioxide production (VCO_2) change as a function of growth/maturation as well as disease. These papers have established normative data that can be used for the present study. There is also a growing understanding that the field of pediatrics is transforming from one that deals with acute disease to one that need to deal with environmental changes (e.g. sedentary behavior, physical inactivity) and chronic conditions (e.g. obesity) in the 'healthy children' as well as the of chronically ill children who are facing health impairment across the life span. Exercise testing biomarkers in adult medicine are increasingly seen as predictors of quality of life, exacerbation of disease, and even predictors of mortality. It is clear, however, that the current protocols that are used for exercise testing in children are inadequate and are often unsuitable to the particular disease state of the children that needs it most.
Most of the exercise studies are done on a treadmill or stationary bicycle with no ability to compare these two protocols in the same subject (sometimes done in the same laboratory).
Our most recent research was published in 2014 which was our study on how submaximal slopes of gas exchange and HR variables derived during traditional cardiorespiratory exercise testing were of immense value and perhaps even more useful in evaluate cardiorespiratory function that was the traditional cardiorespiratory test.
We plan now on extending the observation to novel protocols that will permit us to more accurately

define on and off transit and recovery times in relatively brief, fun, exercise testing in children and compare it to young adults.

3. Describe the purpose, specific aims or objectives. Specify the hypotheses or research questions to be studied.

Primary Aim:

1. Identify gas exchange kinetics during submaximal exercise bouts and rest periods in different workloads and exercise protocols in children and young adults.
2. To develop a mathematical model to predict and compare gas exchange and heart rate kinetics in response to different protocols of exercise (cycle ergometer and treadmill).

Exploratory Aims:

1. Identify accurate workloads for ramp protocols in children based on adult treadmill ramp protocols.
2. Based on # 1, develop a treadmill ramp protocol to assess peak oxygen consumption (VO_2) based on known workloads in children and young adults.
3. Study the association between body composition and muscle mass (assessed by ultrasound and DXA) and gas exchange kinetics.
4. Study the association between puberty and gas exchange kinetics.
5. Study the association between physical activity and gas exchange kinetics.
6. Identify breathing patterns during rest and exercise.
7. Based on #6, evaluate optimal sensor position to increase sensitivity and specificity.

4. Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims.

Our key outcome variables will be:

Primary:

Breath by breath gas exchange (e.g. VO_2, VCO_2, Minute ventilation (VE)) and HR values and kinetics in response to exercise. The raw breath by breath data will be used to derive response times for on transient and off transient exercise bouts and best fit parameters from mathematical modeling.

Secondary:

1) Physical activity questionnaire – Total score.
2) Godin Leisure Time Exercise questionnaire – Total score
3) Body composition (DXA) – Lean body mass, fat percentage, fat free mass, Bone mass.
4) Muscle mass (Ultrasound)
5) Growth and Development questionnaire – Rating of a pubertal status.
6) **Measurement of Tissue Oxygenation – Concentrations of oxi/deoxygenated hemoglobin in the tissue.**
7) Measurement of breath rate and lung volume.

5. List up to ten relevant references/articles to support the rationale for the research. Do not append an extensive NIH-grant-style bibliography.

1. Davis JA, Whipp BJ, Lamarra N, Huntsman DJ, Frank MH, Wasserman K. Effect of ramp slope on determination of aerobic parameters from the ramp exercise test. Med Sci Sports Exerc.;14(5):339-43, 1982

2. Porszasz J, Casaburi R, Somfay A, Woodhouse LJ, Whipp BJ. A treadmill ramp protocol using simultaneous changes in speed and grade. Med Sci Sports Exerc.35(9):1596-603, 2003
3. Baraldi E, Cooper DM, Zanconato S, Armon Y. Heart rate recovery from 1 minute of exercise in children and adults. Pediatr Res. 29(6):575-9. 1991
4. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. J Appl Physiol Respir Environ Exerc Physiol. 50(1):217-21. 1981
5. Dan M. Cooper*, Szu-Yun Leu*, Pietro Galassetti, and Shlomit Radom-Aizik. Dynamic Interactions of Gas Exchange, Body Mass, and Progressive Exercise in Children. Med Sci Sports Exerc. 46(5):877-86, 2014
6. Armon Y, Cooper DM, Flores R, Zanconato S, Barstow TJ. Oxygen uptake dynamics during high-intensity exercise in children and adults. J Appl Physiol (1985). 70(2):841-8. 1991
7. Zanconato S, Cooper DM, Armon Y. Oxygen cost and oxygen uptake dynamics and recovery with 1 min of exercise in children and adults. J Appl Physiol (1985).71(3):993-8. 1991 Sep
8. Steele RM, Brage S, Corder K, Wareham NJ and Ekelund U. Physical activity, cardiorespiratory fitness, and the metabolic syndrome in youth. J Appl Physiol 105: 342-351, 2008.
910. PPG Grant: Mechanisms of Health Effects of Exercise in Children–Project I Page 131 (figure), page 137 (Barrier → Solution), Page 143 ("Exercise Challenge").
10. Associations of cardiorespiratory fitness in children and adolescents with physical activity, active commuting to school, and screen time. Aires L, Pratt M, Lobelo F, Santos RM, Santos MP, Mota J. J Phys Act Health. 2011 Sep;8 Suppl 2:S198-205
11. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. J Appl Physiol. 1984;56:626 –34.
12. Midorikawa T, Ohta M, Hikihara Y, Torii S, Sakamoto S.
Prediction and validation of total and regional skeletal muscle volume using B-mode ultrasonography in Japanese prepubertal children. Br J Nutr. 2015 Oct 28;114(8):1209-17.
13. Eliakim A, Burke GS, Cooper DM. Fitness, fatness, and the effect of training assessed by magnetic resonance imaging and skinfold-thickness measurements in healthy adolescent females. Am J Clin Nutr. 1997 Aug;66(2):223–231

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

1. List all research team members who will interact or intervene with human subjects or will have access to identifiable private information about human subjects. *Include additional rows for Co-researchers and Research Personnel, as needed.*
2. For each research team member, indicate all applicable research activities the individual will perform. *Finalizing informed consent is reviewing, answering/asking questions, confirming competency, as necessary, and signing/confirming the informed consent.*
3. If applicable, list the Faculty Sponsor as a Co-Researcher who will have research oversight responsibilities.

Lead Researcher:

Name and Degree: Dan M. Cooper, MD

Position/Title and Department: Associate Vice Chancellor for Clinical Translation Science

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Cooper is a board certified pediatrician and pediatric pulmonologist who has

been actively involved in NIH-funded research since 1978. He is currently the Director of the UCI Institute of Clinical and Translational Science. Dr. Cooper's area of expertise is in the developmental biology of exercise response, and has published extensively in exercise testing, training programs in children and adolescents, hormonal response to exercise in both children and adults. Dr. Cooper has extensive experience in the recruitment of subjects, the consent process, exercise challenges in children, the treatment of asthma, and in data analysis. As the Lead Researcher, Dr. Cooper is responsible for the entire conduct of the study, and he will supervise all aspects of the research project.

Co-Researcher:

Name and Degree: Shlomit Radom-Aizik, PhD

Position/Title and Department: Assistant Professor, Department of Pediatrics

Team Member will: **[ ]** serve as Faculty Sponsor with research oversight responsibilities

[X] Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individualeserelevant qualifications (training, experience): Dr. Shlomit Radom-Aizik received her MSc. Degree in Physiology and Pharmacology from Tel Aviv University, Sackler Faculty of Medicine, in the field of exercise physiology, and completed her PhD dissertation in the Functional Genomics Unit at Sheba Medical Center, Tel Aviv University, Israel.rsity, Sackler Faculty of Medicine, in the field of exercise physiology, and completed her of Clinical and Translational Science. Dr. Cooper's area of experce Human Performance Laboratory. Her research focuses mainly on functional genomics and exercise physiology and includes: immune system and muscle genomic and epigenetic responses to exercise, effects of exercise and training during childhood and adolescence, effects of exercise and training on children with chronic diseases and children with special needs. Dr. Radom-Aizik will be involved in screening and recruiting, finalizing informed consent, research activities and will have access to subject identifiable data.

Co-Researcher:

Name and Degree: Ronen Bar-Yoseph, M.D.

Position/Title and Department: Visiting Scholar, Department of Pediatrics

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Ronen Bar-Yoseph received his medical degree (Cum Laude) in 2002, from the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel. Dr. Bar-Yoseph is a senior Pediatric Pulmonologist, and the head of the Children's Physical Activity and Nutrition Clinic in Rambam Medical Center, Haifa, Israel. Dr. Bar Yoseph is currently a Visiting Scholar in the Pediatric Exercise and Genomics Research Center (PERC). Dr, Bar-Yoseph will be involved in screening and recruiting, finalizing informed consent, research activities and will have access to subject identifiable data.

Co-Researcher:

Name and Degree: Jen Jen Chen, MD

Position/Title and Department: Clinical Assistant Professor, Pediatrics

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[ ] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Clinical Assistant Professor, Pediatric Exercise and Genomics Research Center, Department of Pediatrics. Dr. Chen completed her Fellowship in Pediatric Pulmonary at University of California, Irvine in June of 2014. Dr. Chen is board certified in Pediatrics and in Pediatric Pulmonary. Dr. Chen will be involved with data analysis.

Co-Researcher:

Name and Degree: Kim Lu, MD

Position/Title and Department: Clinical Assistant Professor, Pediatrics

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Clinical Assistant Professor, Pediatric Exercise and Genomics Research Center, Department of Pediatrics. Dr. Lu completed her Fellowship in Pediatric Pulmonary at Johns Hopkins University in June of 2013. Dr. Lu is board certified in Pediatrics and Pediatric Pulmonary. Dr. Lu will be involved in research activities (exercise protocols) and will have access to subject identifiable data. She will not be involved with the informed consent process or recruitment.

Co-Researcher:

Name and Degree: Abraham Chiu, BS

Position/Title and Department: PhD-tract graduate student in the department of pharmacology

Team Member will: [ ] Screen/Recruit [ ] Finalize Informed Consent

[X] Perform Research Activities (describe below) [X] Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Mr. Chiu is a PhD-tract graduate student in the department of pharmacology under the advisement of Drs. Dan Cooper and Shlomit Aizik and will perform research activities (non-invasive ultrasound and tissue oxygenation measurements (TRS, DOS)). As a part of Mr. Chiu PhD training he was mentored by Dr. Goutham Ganesan who completed his PhD thesis using the TRS and DOS techniques. Mr. Chiu will have access to subject identifiable data. He will not be involved with the informed consent process or recruitment.

Co-Researcher:

Name and Degree: Robert Warren

Position/Title and Department: PhD Student at the Beckman Laser Institute

Team Member will: [ ] Screen/Recruit [ ] Finalize Informed Consent

[X] Perform Research Activities *(describe below)* [X] Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Mr. Warren is a PhD Student at the Beckman Laser Institute. As a part of Mr. Warren's PhD training he has been performing hundreds of TRS and DOS measurements for various IRB protocols. He will be responsible for the operation of the tissue oxygenation measurements (TRS, DOS). He will be present during the exercise tests of the subjects. Mr. Warren will have access to subject identifiable data. He may have interaction with research subjects and access to deidentified research data, but he will not have access to subject PHI and medical records. He will not be involved in subject recruitment or the informed consent process.

Co- Researcher:

Name and Degree: Michelle Khine, Ph.D

Position/Title and Department: Professor, Biomedical Engineering

Team Member will: [ ] Screen/Recruit [ ] Finalize Informed Consent

[x] Perform Research Activities *(describe below)* [x] Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Khine is a faculty collaborator whose laboratory will provide the respiratory sensor to UC Irvine Pediatric Exercise and Genomics Research Center (PERC) and she will supervise the work with this device.

Research Personnel:

Name and Degree: Peter Horvath, Ph.D

Position/Title and Department: Study Coordinator, Pediatrics

Team Member will: [X] Screen/Recruit [ ] Finalize Informed Consent

[X] Perform Research Activities *(describe below)* [X] Access subject identifiable data

Peter Horvath Ph.D.- Dr. Horvath completed his graduate studies at the University of California, Irvine. In his research, he investigated the effects of glucose, lipid, and a combination of glucose and lipid on the white blood cells of healthy, obese and type II diabetic subjects. Dr. Horvath is currently 50% effort study coordinator in the Pediatric Exercise and Genomics Research Center (PERC) and will be involved in data collection, data entry and storage. Dr. Horvath will have access to subject identifiable data and will serve as the administrative contact.

Research Personnel:

Name and Degree: Hoang Ngoc Pham, MS

Position/Title and Department: Pediatrics

Team Member will: [ ] Screen/Recruit [X] Finalize Informed Consent

[X] Perform Research Activities *(describe below)* [X] Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Mr. Pham received his Master of Science in Kinesiology from California State University Fullerton. He will be responsible for performing the exercise testing. Mr. Pham will be involved in finalizing informed consent, research activities and will access subject identifiable data.

Research Personnel:

Name and Degree: Bridgette Duarte, B.S.

Position/Title and Department: Pediatrics

Team Member will: [ ] Screen/Recruit [ ] Finalize Informed Consent

[X] Perform Research Activities *(describe below)* [X] Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Ms. Duarte holds a degree in Nutritional Science, and is currently RD eligible and is part of the Bio-nutrition Research Group for UCI ICTS- PERC. She has been involved in a large number of metabolic studies in children and adults. She is licensed in X-Ray Bone Densitometry and will be responsible for performing the DXA scans on the participants, the food records data collection and analysis.

Research Personnel:

Name and Degree: Annamarie Stehli, MPH

Position/Title and Department: Principal Statistician, Pediatrics

Team Member will: [ ] Screen/Recruit [ ] Finalize Informed Consent

[X] Perform Research Activities *(describe below)* [X] Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Ms. Stehli is Principal Statistician in the Department of Pediatrics and a member of the UCI's Pediatric Exercise and Genomics Research Center (PERC). She obtained her MPH in Epidemiology/Biostatistics from the University of California, Berkeley. She has worked in the Department of Pediatrics since 2002, providing statistical and data management support on many inter-disciplinary projects. Ms. Stehli's research areas include exercise physiology, physiology of stress, neurodevelopmental disorders, maternal and child health, human growth trajectories, intervention studies, and longitudinal data analysis. Ms. Stehli will manage the database, have access to subject identifiable data, and will be involved with data analysis. Ms. Stehli will not be involved in recruitment or the consent process.

Research Personnel:

Name and Degree: Pearl Lynne Law, undergraduate

Position/Title and Department: Bio 199 student in public health science

Team Member will: [X] Screen/Recruit [ ] Finalize Informed Consent

[ ] Perform Research Activities *(describe below)* [X] Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Ms. Pearl Law is a Bio 199 student. Ms. Law will be assisting participant

recruitment, data collection and data entry. Ms. Law will have access to subject identifiable information. She will not be involved with the informed consent process or perform research activities.
Research Personnel : Name and Degree: Thao Nguyen, Ph.D. Student Position/Title and Department: Graduate Student Researcher, Chemical Engineering and Material Science Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent **[x]** Perform Research Activities *(describe below)* **[X]** Access subject identifiable data List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Thao will be adhering the sensors onto subjects, instructing the subject on the testing procedure, and acquiring the data from the sensor.
Research Personnel: Name and Degree: Michael Chu, Ph.D. Student Position/Title and Department: Graduate Student Researcher, Biomedical Engineering Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent **[x]** Perform Research Activities *(describe below)* **[X]** Access subject identifiable data List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Michael will be adhering the sensors onto subjects, instructing the subject on the testing procedure, and acquiring the data from the sensor.

SECTION 3: SUBJECT POPULATION(S) (INDIVIDUALS/RECORDS/SPECIMENS)

A. Subjects To Be Enrolled on this UCI protocol (Persons/Records/Biospecimens)

1. Complete the table of subject enrollments below. *Include additional rows for subject category/group, as needed.*
2. If the study involves the use of existing records or biological specimens, specify the maximum number to be reviewed/collected and the number needed to address the research question.

Category/Group (e.g., adults, controls, parents, children)	**Age Range (years)** (e.g., 7-12, 13–17, adults)	**Maximum Number to be Consented or Reviewed/Collected** (include withdrawals and screen failures)	**Number Expected to Complete the Study *or Needed to Address the Research Question***
Early and late pubertal boys (Tanner 1-5)	7-17	53	35
Early and late pubertal girls (Tanner 1-5)	7-17	53	35
Young adult women	18-35	37	10

Young adult men	18-35	37	10
		Total: 180	90

B. Overall Study Sample Size

If this is a multi-site study, provide the total number of subjects to be enrolled from all sites.

[X] Not applicable: This study will only take place at UCI, and does not involve other sites.

Total number of subjects across all sites: <Type here>

C. Eligibility Criteria

1. Identify the criteria for inclusion and exclusion.

Healthy Children
Inclusion Criteria:

- Between the ages of 7-17 years old without any known respiratory, cardiac or metabolic disease
- Determined to be in good health by preparticipation history
- No evidence of disease or disability that would impair participation in an exercise testing
- No chronic prescribed medication

Exclusion Criteria:

- Other limitation which in the eyes of the physician that would preclude ability to perform exercise testing
- Use of illegal drugs or abuse of alcohol
- Pregnancy or breastfeeding

Healthy young adults
Inclusion Criteria:

- Between the ages of 18-35 years old without any known respiratory, cardiac or metabolic disease
- Determined to be in good health by preparticipation history
- No evidence of disease or disability that would impair participation in an exercise testing
- No chronic prescribed medication

Exclusion Criteria:

- Pregnancy or breastfeeding
-
- Other limitation which in the eyes of the physician that would preclude ability to perform exercise testing
- Use of illegal drugs or abuse of alcohol

2. If eligibility is based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only), provide a scientific rationale.

[ ] Not applicable: Subject eligibility is not based on these factors.

This study will be limited to Children aged 7-17 years and Young Adults aged 18-35 years. The choice of studying young children/adolescents is due to the lack of information regarding the effect of acute bout of exercise and repeated bouts of exercise (which mimic the real life behavior of kids), in this specific age group. Few studies have been performed on adults looking at some aspects that we cover in this study,

but results may not apply to children/adolescents, who present marked differences with adults.

Pregnancy/childbearing potential – This study involves physiologic responses that can change through the pregnancy. It is still not fully known the effects of vigorous exercise at the first trimester on the fetus. The effects of DXA to an unborn fetus, should a female subject be pregnant, are unknown, therefore pregnant individuals will be excluded.

SECTION 4: RECRUITMENT METHODS

Check any of the following methods that will be used to recruit subjects for this study:

[ ] This study involves no direct contact with subjects (i.e., use of existing records, charts, specimens).

Specify database or IRB-approved protocol number (HS#), if applicable: <Type here>

[X] Advertisements, flyers, brochures, email, Facebook, and/or other media.

Specify where recruitment materials will be posted: Participants will be recruited through flyer distribution, and through other studies being conducted on campus. Flyers will be placed in the waiting room at the ICTS in Orange and at Hewitt Hall (main campus). Flyers and provision of direct information to potential subjects will take place in schools

Submit recruitment materials for IRB approval.

[X] The study will be listed on Clinicaltrials.gov. *All clinical research must be registered.*

[ ] The study will be listed on the UC Irvine Health Clinical Trials web page.

Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.

[ ] The UCI Social Sciences Human Subjects Lab/Sona Systems will be used.

Submit the Social Science Human Subject Pool Recruitment Advertisement for IRB approval.

[ ] Referral from colleagues

- Study team will provide colleagues with UCI IRB-approved recruitment materials for distribution to potential subjects (e.g., recruitment flyer, introductory letter);
- An IRB-approved recruitment letter will be sent by the treating physician. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members; and/or
- Colleagues obtain permission from interested patient to release contact information to researchers.
- Study team does not have access to patient names and addresses for mailing.
- If colleagues will screen their patients' medical records to determine subject eligibility and approach patients directly about study participation: *Complete Appendix T to request a partial waiver of HIPAA Authorization.*

Submit recruitment materials for IRB approval.

[X] Study team will contact potential subjects who *have given prior permission to be contacted* for research studies.

Specify when and how these individuals granted permission for future contact: Participants granted permission for future contact when they were screened for other studies conducted at PERC. Specifically, at the time of screening participants were asked if study team members could contact them for future research.

Specify database or IRB-approved protocol number (HS#): HS# 2012-9253, HS# 2010-7943

[X] Study team members will approach their own patients, students, employees for participation in the study.

[ ] Study team will screen UCIMC medical records to which they have access to determine subject eligibility. The patients' physicians will approach patients directly about study participation.

Complete Appendix T to request a partial waiver of HIPAA Authorization.

[ ] Other Recruitment Methods: <Indicate the recruitment method(s) here>

SECTION 5: INFORMED CONSENT PROCESS

A. Methods of Informed Consent

1. Indicate all applicable informed consent methods for this study. *Submit the consent/assent document(s) with your e-IRB Application (e.g., Study Information Sheet, Recruitment script, Consent Form, etc.). Only IRB approved consent forms (containing the IRB approval footer) may be used to consent human subjects at UCI.*

[X] **Written (signed) informed consent will be obtained from subjects.** Signed informed consent, parental permission, and/or child assent will be obtained from subjects, as applicable.

[ ] **Requesting a waiver of written (signed) informed consent.** Signed consent will not be obtained; consent will be obtained verbally or via the web. Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable.

Complete Appendix P.

[ ] **Requesting to seek surrogate consent from a legally authorized individual.** Surrogate consent may be considered only in research studies relating to the cognitive impairment, lack of capacity or serious or life-threatening disease and conditions of the research subjects.

Complete Appendix E.

[ ] **Requesting a waiver of informed consent.** (i.e., consent will not be obtained). *Skip to Section 5.B.*

Complete Appendix O.

2. Indicate where the consent process will take place.

[X] In a private room
[ ] In a waiting room
[ ] In an open unit
[ ] In a group setting
[ ] The internet
[ ] In public setting
[ ] Over the phone
[ ] Other (specify):

3. Specify how the research team will assure that subjects have sufficient time to consider whether to participate in the research.

[X] Subjects will be allowed to take home the unsigned consent form for review prior to signing it.

[ ] Subjects will be allowed <Type here> hours to consider whether to consent.

[ ] Other (specify): <Type here>

4. If children are enrolled in this study, describe the parental permission process and the child assent process.

[ ] Not applicable: Children are not enrolled in this study.

For adolescents and children, consent will be obtained from their parents or legal guardians and assent will be obtained from the children themselves. We meet with potential volunteers and their parents/guardians in a private consulting room where there is no disturbance or distraction from other ongoing clinical activities. Each child and appropriate guardian will meet with designated study staff and the protocol will be explained in detail. It is our experience that this process requires about 20-30 minutes. We then ask the potential study volunteer and his or her guardians to review the written Consent form. Our staff indicates that they will be outside the consulting room should the child or guardian(s) have questions. This process usually takes about 10 minutes. We then ask the potential volunteer and guardians if they have additional concerns or questions and whether or not they wish to

participate in the study. The whole process typically takes about 45 minutes.

The ICTS Clinical Research Center is modeled after a doctor's office. There is a comfortable waiting area with a receptionist who monitors information flow in the unit. Names of individuals are used discreetly by the receptionist. All charts remain in the control of the physicians and key personnel.

5. Some subjects may be vulnerable to coercion or undue influence, such as those who are economically or educationally disadvantaged, mentally disabled, or students (undergraduate, graduate, and medical students) and employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.), describe the procedures to ensure the voluntary participation of these individuals.

[ ] Not applicable: Subjects are not vulnerable to coercion or undue influence.

[X] Other (specify): Children and adolescents may be vulnerable to undue influence. In order to proceed with the study, a consent must be signed by the participants and their parents or guardians. Children and guardians will be protected from undue influence by properly explaining and discussing study procedures and answering their questions. The children and guardian will be informed that by refusing to sign the consent will not affect any continuum of medical care. We make every effort to ensure that the parent/guardian and child or adolescent understands that they do not need to agree to participate and should only do so if they are comfortable with the protocols and procedures in the study. Over many years of working with children and their parents, we believe we have never unduly influenced a child or caregiver to agree to a study that they themselves did not willingly want to participate in.

B. Health Insurance Portability and Accountability Act (HIPAA) Authorization

Indicate all applicable HIPAA authorization methods for this study.

[ ] Not applicable: Study does not involve the creation, use, or disclosure of Protected or Personal Health Information (PHI).

[ ] **Requesting a Total waiver of HIPAA Authorization.** HIPAA authorization will not be obtained at all for the study.

STOP *Complete Appendix T.*

[ ] **Requesting a Partial waiver of HIPAA Authorization.** HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.

STOP *Complete Appendix T.*

[X] **Written (signed) HIPAA Research Authorization will be obtained from subjects.** Signed authorization, parental authorization, and/or child assent will be obtained from subjects, as applicable.

STOP Complete the HIPAA Research Authorization form.

C. Methods of Informed Consent for non-English Speakers

1. Indicate the applicable informed consent method for non-English speakers.

[ ] Not applicable: Only individuals who can read and speak English are eligible for this study. *Scientific justification must be provided in Section 3.C.2.*

[X] The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. *The translated consent form must be submitted to the IRB for review prior to use with human subjects. Only IRB approved consent forms (containing the IRB approval stamp) may be used to consent human subjects at UCI.*

[ ] Requesting a short form consent process.

STOP *Complete Appendix Q.*

The short form process will be used for the following occasional and unexpected languages:

[ ] All non-English languages
[ ] All non-English languages except Spanish
[ ] Other languages (specify): <Type here>

2. Explain how non-English speaking subjects will be consented in their language and who will be responsible for interpreting and facilitating the informed consent discussion for the non-English speaking subjects.

[X] At least one member of the study team is fluent in the language that will be used for communication, and that study team member(s) will be available during emergencies.

STOP *For all members of the study team responsible for obtaining informed consent from non-English speaking subjects, provide their qualifications to serve in this capacity (i.e. language fluency) in Section 2.*

[ ] The study team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study.

[ ] Other (explain): <Type here>

SECTION 6: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Location

Specify where the research procedures will take place (e.g. UCI Douglas Hospital – Cardiac Care Unit, UCI Main Campus Hewitt Hall, UCI Health – Pavilion II, UCI Family Health Center, Anaheim, Irvine High School).

STOP *If research activities will also be conducted at non-UCI locations (e.g., educational institutions, businesses, organizations, etc.), Complete Appendix A. Letters of Permission or other documentation may be required (e.g. Off-site Research Agreements or IRB Authorization Agreements).*

Research procedures will take place at the PERC-ICTS Human Performance Laboratory at the UCI Main Campus- Hewitt Hall, UCI Medical Center, and the Pediatric Exercise and Genomic Research Center (PERC) located at 101 Academy, Suite 150 in Irvine (Research Park).

B. Study Design

1. Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme.

Cross-sectional study. Each child will be asked to participate in up to 6 exercise sessions. Each session will require no more than 2 hours.
Each participant will complete an assessment that will include a cycle ergometer ramp protocol (session 1A) and ten by 2 exercise (session 1B). Data collected from this assessment will be used to configure the rest of the exploratory sessions and development of the treadmill protocol. Sessions 2 and 3 will be done by all participants, however the order of these sessions (i.e. session 2 before session 3; or session 3 before session 2) will be randomized.

2. Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived.

1) Gas exchange values (e.g. - Oxygen uptake (VO_2), Carbon dioxide production (VCO_2), Minute ventilation (VE)) and kinetics measured by the metabolic cart.
2) HR by EKG.
3) Work load from the ergometer.
4) Puberty status from the Growth and Development questionnaire.
5) Physical activity status from the Physical activity questionnaire, Godin Leisure Time Exercise questionnaire and the Determination of Physical Activity Readiness Code.
6) Body composition based upon DXA measurements.
7) Muscle mass based upon ultrasound measurements.
8) **Concentrations of oxi/deoxygenated hemoglobin in the tissue based upon Tissue Oxygenation measurements.**

C. Research Procedures

1. Provide a detailed chronological description of all research procedures.

Each child will be asked to participate in up to 6 exercise sessions. Each session will require no more than 2 hours.
Each participant will complete an assessment that will include a cycle ergometer ramp protocol (session 1A) and ten by 2 exercise (session 1B). Data collected from this assessment will be used to configure the rest of the exploratory sessions and development of the treadmill protocol. Sessions 2 and 3 will be done by all participants, however the order of these sessions (i.e. session 2 before session 3; or session 3 before session 2) will be randomized.

Session 1: Fitness Assessment and screening

Session 1A:
Each child or young adult will be asked to complete Physical activity questionnaire, Godin Leisure Time Exercise questionnaire and Determination of Physical Activity Readiness Code - a series of questions to determine participation in physical activity or sport.

Exercise test - Exercise testing will be performed at the UCI PERC-ICTS Human Performance Laboratory. To measure cardiorespiratory responses to exercise and assess fitness, we will use a ramp-type progressive exercise test on an electronically braked cycle ergometer (SensorMedics Ergoline 800S, Yorba Linda, CA) (1), through a method previously designed for children and

adolescents (2). The work rate will increase by 10 W per min (or adjusted according to the subject's age and fitness level) so that the total exercise time will roughly equal 8-12 min, and each subject will exercise to the limit of his or her tolerance. During the exercise tests described here in Sessions 1, 2, and 3, each subject will breathe through a mouthpiece, a nose clip will be worn, and measurements of their breath will be taken. Gas exchange will be measured breath-by-breath using a metabolic cart (SensorMedics VMax 229, Yorba Linda, CA) (3). The metabolic cart measures inhaled as well as exhaled carbon dioxide and oxygen by use of a mouthpiece and nose clip allowing gas exchange measures in the breath. Heart rate will be monitored using special wires that will be attached to the skin of the chest. After exercise, participant's heart rate will be monitored until it reached pre-exercise values. If any faintness or dizziness is reported, participants are asked to lay down and are then allowed to leave after 30-min of cessation of symptoms. This approach has been used extensively in our laboratory in children, adolescents and adults. At the end of the exercise protocol the participant is asked to rate his perceived exertion (RPE).

Growth and Development questionnaire - Children will be asked to fill a standard self-assessment Tanner staging questionnaire; this questionnaire is currently used by our group in several UCI IRB apporved studies, and a copy is appended to this application.

Dual X-ray Absorbiometry (DXA) – Each participant will perform one DXA assessment. Each DXA, subjects will undergo a total of 3 scans: a complete body scan, a hip scan, and spine scan. Total and regional body composition will be measured by dual-energy X-ray absorptiometry (DXA) using a Hologic densitometer. Measurement of body composition using DXA is based on the exponential attenuation due to absorption by body tissues of photons emitted at two energy levels (40 and 70 keV). Subjects will be asked to lie on their backs on a padded table wearing normal clothes with metal objects removed. The counter moves in a raster pattern above the subject's body from head to foot and counts attenuation rates of photons emitted from the X-ray source within the table. The total dose for a scan is less than several hours of background exposure (1-4 millirem per DXA scan). DXA provides estimates of the following parameters: bone mineral densities (BMD; g/cm2), soft-tissue attenuation ratios, fat and lean tissue weights (g), and bone mineral weight. These parameters can be recorded for the whole body or in any number of defined anatomical regions of interest. DXA scanning involves x-ray dose at minimal levels. Technicians do not wear shielding, nor do subjects require shielding during the procedure. Female subjects capable of having children (regardless of age) will be asked to provide a small urine sample prior to the DXA scan. Results of the pregnancy test will be disclosed to either the parent or the legal guardian with the child's permission and/or the participant for subjects less than 18 years of age. Results of the pregnancy test will be disclosed to female subjects 18 years of age or older.

Ultrasound – Noninvasive measurements of muscle size will be made using ultrasound of the leg or arm. These studies require only a few minutes, are noninvasive, do not hurt, and have no known side effects (ultrasound will also be done in session 2 and 3).

Respiratory sensors – Breathing patterns (breath rate and volume) will be evaluated by a non-invasive ultrasensititve piezoresistive strain sensors capable of measuring large mechanical strains of the chest during breathing. The sensors have a form factor of a disposable BandAid© and will be worn on the upper torso during rest and exercise. This measurement is noninvasive, do not hurt, and have no known side effects.

Session 1B:

Exercise will take place not before 48 hours and no later than 4 weeks after visit 1. This is performed on a stationary bicycle for ten, 2-min period of exercise (bout) at a constant work rate with 1-min resting intervals between each exercise period. Of course, the participant can come off the mouthpiece and stop exercising whenever he or she desires. Ultrasound measurement of muscle size—See above.

Non-invasive measurement of Tissue Oxygenation:
All exercise sessions described above will use a variety of non-invasive measurements of tissue oxygenation. These measurements are described below.
DOS - Superficial tissue hemoglobin, water, and lipid content will be measured using two Diffuse Optical Spectroscopy (TRS21, mDOSI) devices. These instruments use near-infrared (NIR) light to measure tissue optical properties in a safe, non-invasive manner. For example, the pulse oximeter is a similar commercial instrument that uses a similar technique and has found wide clinical acceptance.d re DOS optical devices uses visible and NIR light the other near-infrared, to measure the arterial hemoglobin saturation, water, and lipid content of superficial tissue. The devices differ in how often measurements are taken in order to better understand differences in tissue composition: 1) TRS21, developed by Hamatasu Photonics, Japan and 2) mDOSI, develop at UCIrinve Beckman Laser Institute. DOS will be used to monitor muscle and bone tissue optical properties (arms, legs, forehead, torso and abdomen) at the PERC Exercise Lab before (~ 5 minutes at baseline), during, and after exercise (~ 5 minutes). The only part of the DOS apparatus in contact with the participant will be the optical probe containing two fiber optics held together with plastic, silicone/rubber and metal. NIR light will enter the tissue through one set of optical fibers. Reflected light that has sampled underlying tissue (skin, muscle, microvasculature, subcutaneous fat and fascia) will be collected via the other set of optical fibers (DOS will also be done in session 2 and 3)

<u>Session 2: Cycle ergometer exercise with different work rate intensities</u>

Exercise will be performed on a stationary bicycle. Exercise will consist of up to ten, exercise bouts at a constant work rate with resting intervals between each exercise period for a total of approximately 30 minutes or a ramp protocol. The exercise will be at different levels of intensity (easy, moderate, and hard and depend on the results in session 1) and the rest and exercise duration will vary. Of course, the participant can come off the mouthpiece and stop exercising whenever he or she desires.
Ultrasound measurement of muscle size—See above.
Non-invasive measurement of Tissue Oxygenation - See above

<u>Session 3: Treadmill exercise with different work rate intensities</u>

The treadmill exercise protocol will include changes in the level of exercise (easy, moderate, or hard and depend on the participant results in Session 1). The total exercise time for this portion of the study is approximately 30 minutes. Of course, the participant can come off the mouthpiece and stop exercising whenever he or she desires. Ultrasound measurement of muscle size—See above.
Non-invasive measurement of Tissue Oxygenation - See above

REFERENCES

Whipp BJ, Davis JA, Torres F, Wasserman, K. A test to determine parameters of aerobic function during exercise. J Appl Physiol. 1981;50:217–21.

Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. J Appl Physiol. 1984;56:626 –34.

Beaver WL, Lamarra N, Wasserman K. Breath-by-breath measurement of true alveolar gas exchange. J Appl Physiol. 1981;52:1662–75.

2. Describe the duration of a subject's participation in the study. If there are sub-studies, include duration of participation in each sub-study.

We will ask the participant to participant in up to 6 exercise sessions over the course of 12 weeks. It is anticipated that each session will require no more than 2 hours.

3. List data collection instruments (e.g., measures, questionnaires, interview questions, observational tool, etc.).

Investigator-authored, non-standardized, or un-validated measures must be submitted for review.

Growth and Development questionnaire - Children will be asked to fill a standard self-assessment Tanner staging questionnaire; this questionnaire is currently used by our group in several UCI IRB approved studies, and a copy is appended to this application.

Physical activity questionnaire: Children will be asked to fill a standard self-assessment Physical activity questionnaire; this questionnaire is currently used by our group, and a copy is appended to this application

Godin Leisure Time Exercise questionnaire: Children will be asked to fill a standard self-assessment Physical activity questionnaire; this questionnaire is currently used by our, and a copy is appended to this application

Determination of Physical Activity Readiness Code: Children will be asked a standard self-assessment Physical activity questionnaire; this questionnaire was used by the NHANES (National Health and Nutrition Examination Survey - a program of studies designed to assess the health and nutritional status of adults and children in the United States), and a copy is appended to this application

D. UCIMC Supplementary Clinical Services

If a UCIMC clinical unit/department (e.g., phlebotomy for blood draws, pharmacy for dispensing study drug(s), radiation services for X-rays, MRIs, CT scans, and Neurology for lumbar punctures) will perform research-related procedures:

1. List the research procedure (e.g. lumbar puncture, MRI, CT Scan), and
2. Identify the unit/department that will perform the procedure.

[X] Not applicable: This study does not involve the services of a UCIMC clinical unit/department.

<Type here>

E. Privacy

Privacy is about the subject's ability to control how much others see, touch, or collect information about the subject. Indicate all of the following methods that will be used to assure subject privacy. *Violations of privacy include accessing a subject's private information without consent, asking personal sensitive information in a public setting, being audio recorded or photographed without consent.*

[X] Research procedures (including recruitment) are conducted in a private room.

[ ] Use of drapes or other barriers for subjects who are required to disrobe.

[X] Only sensitive information directly related to the research is collected about subjects.

[ ] When information is collected from internet sources, the internet site's privacy statement will be reviewed and followed.

Provide a copy of the Data Use Policy to the IRB.

[ ] Other (specify): <Type here>

F. Use of Existing Biological Specimens and/or Existing Information/Data

1. For studies that involve use of existing (i.e. on the shelf; currently available) specimens:
   a. Indicate the source of the specimens and whether the specimens were originally collected for research purposes.
   b. Explain how the existing specimens will be obtained.

[X] Not applicable: This study does not involve use of existing biological specimens.

Source: Indicate all that apply:

[ ] UCI/UCIMC

Originally collected for research purposes: **[ ]** YES; UCI IRB number (i.e. HS#): <Type here>
[ ] NO; explain: <Type here>

[ ] UCIMC Pathology Biorepository will provide specimens.

[ ] Non-UCI Entity; specify: <Type here>

Originally collected for research purposes: **[ ]** YES

Submit a copy of the IRB Approval Notice and Consent Form for the original collection.

[ ] NO; explain: <Type here>

[ ] Other; explain: <Type here>

2. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data:
   a. Specify the source of the clinical data.
   b. Explain how the study team will access the clinical data. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services.*

For investigator initiated/authored studies only, submit a data abstraction sheet that includes a complete list of data elements/information that will be collected from (existing) records or submit the case report form (CRF; eCRF).

[X] Not applicable: This study does not involve use of existing clinical data. *Skip to Section 6.G.*

Source: Indicate all that apply:
[ ] UCI/UCIMC.
[ ] non-UCI Entity; specify: <Type here>

How Obtained: Indicate all that apply:
[ ] The study team will request specific patient information/data from UCIMC Health Information Management Services.

[ ] The study team will review their patients' records and abstract data directly from those records.

[ ] The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

[ ] Other; explain: <Type here>

3. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data, specify the time frame of the clinical data to be accessed (e.g. records from January 2002 to initial IRB approval).

This study does not involve the use of existing clinical data.

G. Collection of Photographs, or Audio/Video Recording

1. Describe all procedures involving the use and/or collection of photographs, or audio/video recording.

[ ] Not applicable: This study does not involve photographs or audio/video recording. *Skip to Section 6.H.*

Photographs and video recordings will be taken in order to be used in presentations, publications and for training purposes. Photographs and video recordings would not be used for research purposes.

2. Specify if photographs or audio/video recording will include subject identifiable information (e.g., name, facial image). If so, indicate which identifiers will be collected.

Photographs or audio/video recording could include subject identifiable information (study ID, facial and body image).

3. Explain whether the photographs or audio/video recording will be included in subsequent presentations and/or publications and, if so, whether subject identifiers will be included.

Photographs or audio/video recording will be included in subsequent presentations, training and/or publications just upon a signed consent form (participant and parent (if under 18 years old). A copy of the "consent to photograph" form is appended to this application. No names will be attached to the photographs or video recordings.

H. Sharing Results with Subjects

1. Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician). *Only tests ordered by a physician and conducted in a CLIA certified lab may be shared.*
2. Explain what information will be shared and how the results will be shared.

[ ] Not applicable: Individual results will not be shared with subjects.

subjects will receive information such as their level of fitness, bone mineralization, percent body fat and pulmonary function tests

3. Describe whether overall study results will be shared with subjects.
4. Explain how results will be shared.

[X] Not applicable: Final study results will not be shared with subjects.

<Type here>

I. Statistical Considerations *(This section is required for Investigator-Authored Research)*

1. Statistical Analysis Plan: Describe the statistical method(s) for the stated specific aims and hypotheses. *Your analysis plans should match the stated study specific aims and hypotheses in Section 1.*

[ ] Not applicable: A statistical analysis plan is not appropriate for this qualitative study design. Plan for assessing study results: <Type here>
Skip to Section 7.

This is a pilot study that is being conducted to identify gas exchange kinetics during exercise bouts and rest periods in different workloads during treadmill exercise and cycle ergometer. From past research of single exercise bout gas exchange kinetics the following theoretical model, has been proposed to describe VO_2 as a function of time across the bout:

$$G(s) = \frac{Kp}{1+Tp1*s} * \exp(-Td*s)$$

Kp= gain/amplitude; Tp1 = time constant; Td = time delay; s=second of exercise bout

The goal of the current research is to apply this functional form to observed kinetics during repeated exercise bout protocols. Evaluation of the fit of this model to observed kinetics will be performed using the system identification toolbox in Matlab. The modules for modeling of nonlinear dynamic systems will be applied which produces parameter estimates of the fitted model based on maximum likelihood and prediction-error minimization (PEM). Applying this curve fitting tool may also give rise to variations in the proposed model that should be considered. Comparisons of Final Prediction Error and Mean Squared Error will be performed to determine the model with optimal fit. In addition, to address the issue of out of sample generalizability, cross validation analyses will also be employed to assess model performance.
A secondary goal to this research is that once a functional form has been established, comparisons of the distributions of the function's parameters (Kp, Tp1, Td) can be made in relation to participant characteristics such as sex, pubertal status, and developmental stages (e.g, children, adolescence, adults). For example, a significant difference in the average time constant (Tp1) would be interpreted as more efficient oxygen consumption and differential adaptation to the physiologic challenge of exercise.

2. Describe the primary statistical method(s) that will be used to analyze the primary outcome(s) or endpoints.

The data will be used for estimating the mean(s) and standard deviations of gas exchange and HR outcomes within bouts as well as response times. Estimation of the functional form of the relationship of each outcome and time and/or work rate across exercise periods will be conducted by applying theoretical mathematical equations to the data, assessing the fit of these models (e.g., analysis of residuals and observed AUC vs predicted AUC), and determining the best fit parameters using modeling software packages in M+ and SAS.

3. Describe the secondary statistical method(s) that will be used to analyze the secondary outcome(s) or endpoints.

Beyond the univariate statistics described above, comparison of outcomes between the treadmill task and cycle egrometer task will be made to validate exploratory protocols for the treadmill task. These results will be used to generate additional hypotheses to be tested in the subsequent study.

Each subject's bone density and body composition will be measured by a DXA scan at session 1. Ultrasound measurements will be measured at sessions 1-3. Results will be shown using mean and SD.

The standardized questionnaires data will be used to develop measures of subject physical activity and puberty level which will also be statistically analyzed. Regression models will evaluate the relationship between these factors and the performance on the exercise protocols (measured by the primary outcomes)

4. If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis.

<Type here>

5. Sample Size Determination: Explain how the overall target sample size was determined (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint.

To date application of the proposed model has been performed for 5 subjects, hence the primary goal of this project being to obtain more data. The parameter estimates, with their standard errors are presebted below for the 5 participants. In addition percent fit, final prediction error and Mean Square Error of the overall model fit are presented for each participant. The within-subject Root MSE is considered moderate to strong given the range of VO_2 exhibited (.59 to 2.8)

id	KP	KP Std Error	Tp1	Tp1 Std Error	Td	Td Std Error	fit to est data	FPE	MSE	RMSE
1	0.016574	0.00006944	52.33	0.92884	0	0.37017	47.60%	0.0809	0.0806	0.2839
2	0.01867	0.00010643	49.012	1.16360	0	0.48813	40.33%	0.2402	0.2393	0.4892
3	0.014909	0.00045517	48.352	0.74137	0	0.32196	56.26%	0.06836	0.0681	0.2610
4	0.018458	0.00007670	67.049	1.24980	0.061	0.92871	46.52%	0.1198	0.1194	0.3455
5	0.017474	0.00008908	55.46	1.26130	0	0.47396	36.77%	0.09185	0.09144	0.3024

Our
extensive past experience suggests that pilot data from 90 subjects which will be adequate to develop the necessary data set to move this project forward and can be used to design a subsequent larger study.

SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS

A. Risk Assessment

1. Indicate the appropriate level of review of this study, based upon your risk assessment.

[X] This study involves greater than minimal risk to subjects and requires Full Committee review. *Skip to Section 7.B.*

[ ] This study involves no more than minimal risk and qualifies as **Expedited research**.

2. If this study involves no more than minimal risk, provide justification for the level of review and for all applicable Expedited Categories you have chosen.

<Type here>

B. Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts — physical, psychological, social, legal or other. Include an assessment of their expected frequency (e.g., common – 65%, less common – 40%, unlikely – 5%, rare - <1%) and the seriousness (mild, moderate, severe). *A bullet point list is recommended. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality.*

All procedures will be supervised by PERC-ICTS study personnel.

The possible risks and/or discomforts associated with the procedures in this study include:

Common: DXA – Radiation risk from DXA scanner. The UCI radiation safety committee will review this study. The DXA scanner uses x-rays to quantify body composition measurements. Study participants will be exposed to a dose of between 1 to 4 millirem per DXA scan. To minimize risks associated with DXA scan, female subjects of childbearing potential (regardless of chronological age) will be given a urine pregnancy test prior to enrollment and prior to the DXA scan. Pregnant female subjects shall be excluded from the study.

Unlikely: EXERCISE TEST– Exercise testing can cause sweating, muscle soreness, feelings of breathlessness, and nausea or dizziness. In rare instances, exercise tests may cause chest pain, tightness, or a change in vital signs. We have performed over 1,000 exercise tests as described in the protocols with no major complications.

Unlikely: MEASURMENT OF BLOOD PRESURE - Inflation of cuff may cause discomfort or bruising.

Unlikely: ULTRASOUND - Incidental finding: There is a risk of an unexpected finding from your ultrasound. The results will be shared with you and if necessary, you will be referred to your primary care physician or other specialist for additional consultation.

Unlikely: Growth and Development Questionnaire Risks- Participants may feel uncomfortable while answering the growth and development questionnaires about changes in puberty (i.e. under arm, facial and pubic hair growth, breast development, and monthly periods).

Unlikely: POTENTIAL BREACH OF CONFIDENTIALITY – We acknowledge that a breach of confidentiality is an associated risk of participation in this study.

Unlikely: UNFORSEEN RISKS – We acknowledge that there may be unforeseen risks to the participants due to his/her participation in the research study.

Unlikely: mDOSi and TRS - This measurement poses very little risk to patients and investigators. This same general instrumentation has been used in several IRB approved protocols at UCI) without incident. Similar instrumentation has also experienced widespread clinical use in the literature. Near-infrared light does not ionize biological tissue and poses no significant health risk. Since water absorption is low within this spectral range, local heating of the tissue is also minimal. Burns and heat damage are highly unlikely. The optical powers we will use in this study are all far less than those used with surgical lasers meant to incise, ablate, and coagulate tissue. The measurement itself is painless, and does not cause any significant discomfort.
Unlikely: Respiratory sensors - This measurement poses very little risk to patients and investigators. This same general instrumentation has been used in several IRB approved protocols at UCI) without incident (HS#2016-2924). The measurement itself is painless, and does not cause any significant discomfort. There is a low risk of skin irritation or allergic reaction to the silicone substrate as well as to the adhesive tape. If there is an allergy, the sensor will be immediately removed from the skin.

2. Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/ potential discomforts to subjects. *Examples include: designing the study to make use of procedures involving less risk when appropriate; minimizing study procedures by taking advantage of clinical procedures conducted on the subjects; mitigating risks by planning special monitoring or conducting supportive inventions for the study; implement security provisions to protect confidential information.*

Protections against risks to privacy of individuals or confidentiality of the data will be taken in accordance with usual human subjects' research procedures, including: ensuring that all study personnel have completed adequate training in conduct of human subjects' research, coding all data so that participants' data are suitably confidential, and obtaining all data in circumstances that preserve participants' privacy.

To minimize risks associated with exercise test, resting heart rate and blood pressure are obtained prior to exercise. Heart rate is monitored during the exercise. The subject is instructed to stop exercise at any time during the test whenever he/she desires. If a vaso-vagal response occurs, the exercise is stopped and the subject will be placed in a recumbent position until heart rate and blood pressure normalize.

Proper warm-up and other safety procedures will be instituted to minimize the possibility of musculoskeletal injuries. A member of the study team will be present during the exercise test.

To minimize risks associated with the measurement of blood pressure, trained personnel will perform the measurement and time of the blood pressure cuff will be reduced.

The researchers will comply with UCI's Adverse Events/Unanticipated Problems reporting policy and procedures. Unanticipated adverse events: 911 will be called. The IRB will be notified of the event. If it is determined that a serious unanticipated adverse event has occurred, then the study will be modified or terminated. All adverse events and unanticipated problems will be reported according to the UCI IRB reporting requirements via the electronic AE/UP submission module.

C. Potential Benefits

1. Describe the potential benefits subjects may expect to receive from participation in this study. *Compensation is not a benefit; do not include it in this section.*

☐ There is no direct benefit anticipated for the subjects.

The possible benefits the subject may experience from the procedures described in this study include the following: the subject may get information about his/her level of fitness, bone mineralization, percent body fat and pulmonary function tests which can help them in guiding their own programs to improve fitness if necessary and how it may impact their cardiorespiratory health. The information gained from these studies may help doctors in understanding how children respond to exercise as it pertains to fitness level.

2. Specify the expected potential societal/scientific benefit(s) of this study.

The information gained from this project will benefit children and adults by better understanding the effects of different ways of physical activity. The metabolic load imposed by physical activity that mimics real life patterns is dynamic and increases with time. The inability to adequately recover from a previous short exercise bout, particularly in a child with a chronic disease or disability, could hamper the ability of the child to engage in physical activity. Accurate modeling of gas exchange and HR responses to patterns of exercise more closely associated with "real life" could lead to better exercise prescriptions for children with chronic disease or disability.

SECTION 8: ALTERNATIVES TO PARTICIPATION

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable.

[X] No alternatives exist. The only alternative to study participation is not to participate in the study.

[ ] There are routine standard of care alternatives available; specify: <Type here>

[ ] There are other alternatives to study participation; specify: <Type here>

SECTION 9: SUBJECT COSTS

1. Indicate below if subjects or their insurers will be charged for study procedures. Identify and describe those costs.

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 10.*

[X] This study involves interaction/intervention with research subjects; however there are no costs to subjects/insurers.

[ ] This study involves interaction/intervention with research subjects, and there are costs to subjects/insurers: <Type here>

2. If subjects or their insurers will be responsible for study-related costs, explain why it is appropriate to charge those costs to the subjects or their insurers. Provide supporting documentation as applicable (e.g., study procedures include routine (standard of care) procedures; FDA IDE/HDE/IND letter that supports billing to subjects).

[X] Not applicable: The study involves no costs to subjects for study participation.

[ ] Study related costs will be billed to subjects or their insurers for the following reasons: <Type here>

SECTION 10: SUBJECT COMPENSATION AND REIMBURSEMENT

1. If subjects will be compensated for their participation, explain the method/terms of payment (e.g., money; check; extra credit; gift certificate).

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 11.*

[ ] No compensation will be provided to subjects.

[X] Compensation will be provided to subjects in the form of cash/gift certificate.

[ ] Compensation will be provided to subjects in the form of a check issued to the subjects through the UCI Accounting Office. The subject's name, address, and social security number, will be released to the UCI Accounting Office for the purpose of payment and for tax reporting to the Internal Revenue Service (IRS).

[ ] Other: <Type here>

2. Specify the schedule and amounts of compensation (e.g., at end of study; after each session/visit) including the total amount subjects can receive for completing the study. *Compensation should be offered on a prorated basis when the research involves multiple visits.*

   For compensation ≥ $600, subject names and social security numbers must be collected. This information must be reported to UCI Accounting for tax-reporting purposes.

[ ] Not applicable: This study involves no compensation to subjects.

Subjects will be compensated with the following schedule and amounts: The participants will receive $25.00 in cash after completing each session. The total possible compensation is $150.00 for six study visits.

3. Specify whether subjects will be reimbursed for out-of pocket expenses. If so, describe any requirements for reimbursement (e.g., receipt).

[ ] Not applicable: This study involves no reimbursement to subjects.

Subjects will be reimbursed; specify: Subjects will not be reimbursed for any out of pocket expenses, such as parking or transportation fees.

SECTION 11: CONFIDENTIALITY OF RESEARCH BIOSPECIMENS/DATA

A. Biospecimens/Data Storage

1. Indicate all subject identifiers that may be included with the biospecimens or collected for the research study. *If any study-related data will be derived from a medical record, added to a medical record, created or collected as part of health care, or used to make health care decisions the HIPAA policy applies. The subject's HIPAA Research Authorization is required or a waiver of HIPAA Research Authorization must be requested by completing Appendix T.*

[ ] This study does not involve the collection of subject identifiers.

Check all the following subject identifiers will be used, created, collected, disclosed as part of the research:

[X] Names	[ ] Social Security Numbers	[ ] Device identifiers/Serial numbers
[X] Dates*	[X] Medical record numbers	[ ] Web URLs
[X] Postal address	[ ] Health plan numbers	[ ] IP address numbers
[X] Phone numbers	[ ] Account numbers	[ ] Biometric identifiers
[ ] Fax numbers	[ ] License/Certificate numbers	[X] Facial Photos/Images
[X] Email address	[ ] Vehicle id numbers	[ ] Any other unique identifier

[ ] Other (Specify all): <Type here>

* *birth date, treatment/hospitalization dates*

2. Indicate how data will be stored and secured, including electronic data as well as hardcopy data paper records, electronic files, audio/video tapes, biospecimens, etc. *If the research data includes subject identifiable data and/or Protected Health Information, the storage devices or the electronic research files must be encrypted.*

Electronic Data/Files (check all that apply):

[ ] Anonymous data will be maintained; no subject identifiers

[ ] Coded data; code key is kept separate from data in secure location.

[ ] Data includes subject identifiable information. Provide rationale for maintaining subject identifiable info): <Type here>

[X] Data will be stored on secure network server.

[ ] Data will be stored on standalone desktop computer (not connected to network/internet)

[ ] Other (specify here): <Type here>

Hardcopy Data (Records, Recordings, Photographs) and Biospecimens (check all that apply):

[ ] Anonymous biospecimens/data will be maintained; no subject identifiers

[ ] Coded data; code key is kept separate from biospecimens/data in secure location.

[ ] Biospecimens/Data includes subject identifiable information (Provide rationale for maintaining subject identifiable info): <Type here>

[X] Data will be stored in locked file cabinet or locked room.

[ ] Biospecimens will be stored in locked lab/refrigerator/freezer.

[ ] Other (specify here): <Type here>

3. List the location(s) where the data and/or biological specimens will be stored.

Data will be stored in locked files cabinet at PERC located at 101 Academy Suite 150 in Irvine.

4. If subject identifiable data will be transported or maintained on portable devices, explain why it is necessary use these devices. *Only the "minimum data necessary" should be stored on portable devices as these devices are particularly susceptible to loss or theft. If there is a necessity to use a portable device for the initial collection of identifiable private information, the research files must be encrypted, and subject identifiers transferred to a secure system as soon as possible.*

[X] Not applicable: Research data will not be transported or maintained on portable devices.

Research data will need to be maintained on the following portable device(s) for the following reason(s): <Type here>

B. Data and/or Biological Specimens Access

Specify who will have access to subject identifiable data and/or biological specimens as part of this study.

[ ] Not applicable: No subject identifiers will be collected.

[X] Authorized UCI personnel such as the research team and appropriate institutional officials, the study sponsor or the sponsor's agents (if applicable), and regulatory entities such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the National Institutes of Health (NIH).

[ ] Other: <Type here>

C. Data and/or Biological Specimens Retention

Indicate how long subject identifiable data and/or biological specimens, including the subject code key will be retained. *If more than one of the options below is applicable (e.g., the study involves children), records must be kept for the longer period.*

[ ] Not applicable: No subject identifiable research data will be retained.

[ ] Separate code key will be destroyed or subject identifiable information will be removed from the biospecimens and/or data at the earliest convenience, consistent with the conduct of this research. Specify timeframe: <Type here>

[ ] Destroyed once research data is analyzed.

[ ] Destroyed after publication/presentation.

[X] Will be maintained; specify time frame and provide the rationale: Records will be retained for indefinitely. The purpose for the data to be stored is for comparison with similar databases from other investigators and with future studies within our laboratory.

[ ] Will be stored and maintained in a repository for future research purposes.

Complete Appendix M

[] Will be retained for six years as this research involves Protected Health Information (PHI) (e.g., IRB documentation, consent/assent forms – NOT the actual PHI). *Investigators must destroy PHI at the earliest opportunity, consistent with the conduct of this study, unless there is an appropriate justification for retaining the identifiers or as required by law.*

[X] Will be retained for seven years after all children enrolled in the study reach the age of majority [age 18 in California] as this study includes children.

[ ] Will be retained 25 years after study closure as this study involves in vitro fertilization studies or research involving pregnant women.

[ ] Will be retained for two years after an approved marketing application, as this is a FDA regulated study. If approval is not received, the research records will be kept for 2 years after the investigation is discontinued and the FDA is notified.

[ ] Other: <Type here>

D. Photographs, Audio/Video Recordings Retention

1. If subject identifiable audio or video recordings will be collected, specify the timeframe for the transcription and describe retention/destruction plans.

[] Not applicable: Subject identifiable audio/video recordings will not be collected.

[ ] Audio or video recordings transcribed; specify time frame: <Type here>

[X] Audio or video recordings will be maintained; specify time frame: 10 years.

[ ] Audio or video recordings maintained indefinitely; provide the rationale: <Type here>

[ ] Audio or video recordings destroyed; specify time frame: <Type here>

2. If subject identifiable photographs will be collected, describe retention/destruction plans.

[ ] Not applicable: Subject identifiable photographs will not be collected.

[X] Photographs will be maintained; specify time frame: 10 years.

[ ] Photographs maintained indefinitely; provide the rationale: <Type here>

[ ] Photographs destroyed; specify time frame: <Type here>

E. Certificate of Confidentiality

1. Indicate whether a Certificate of Confidentiality (COC) has been or will be requested.

[X] Not applicable: No COC has been requested for this study.

[ ] A COC will be or has been requested for this study. *The COC application must be submitted to the IRB staff for review after IRB approval.*

[ ] A COC has been obtained for this study. The expiration date of this COC is: <Type here>

Provide a copy of the COC Approval Letter.

2. Explain in what situations the UCI study team will disclose identifiable private information protected by a COC.

<Type here>