model to a traditional one-level model. If significant group-level variance does emerge, dummy codes to control site-specific variance will be used to enhance statistical power.

C7d. Missing Data

We will conduct missing data analyses in order to differentiate between data that are missing at random (MAR) and data that are missing related to gender or aspects of the treatment plan (e.g., hormone dosing). If missing data can be regarded as MAR, multiple imputations may be used. If the MAR assumption is not plausible, sensitivity analyses will be conducted to evaluate the impact of MAR violations on analyses by specifying models for non-ignorable missing data mechanisms.

C7e. Power Analysis to Determine Sample Size

Early Pubertal Cohort. Unique to the early puberty cohort is the need to assess the effect of GnRH agonists on bone health (Hypothesis 1c). Although we hypothesize that there is no net change in raw bone density over time (precluding power analysis), it is important to assess nontrivial lags in development compared to age-matched peers. Using G*Power version 3.1.3 to conduct an *a priori* power analysis in a repeated measures MANOVA framework with effect size f=.20 (a moderate effect size equivalent to Cohen's d=.40), alpha=.05, adequate statistical power=.80, and 4 measurement time points, a sample of 73 participants would be sufficient to detect significant decrease in age-matched z-scores over time. Thus, we propose to recruit a sample of **80 evaluable participants in the early puberty cohort**, which will yield comparable power to detect moderate changes in mental health outcomes over time (Hypothesis 1a) and good (.89) power to detect significant differences in metabolic and physiologic lab values of one-third of a standard deviation from clinical cutoffs (Hypothesis 1b).

Late Pubertal Cohort. In the absence of available longitudinal metabolic and physiological data, the proposed study will be powered to assess changes in mental health and psychological well-being (Hypothesis 2a) based on evidence from our preliminary data. Using G*Power version 3.1.3 and conducting an *a priori* power analysis in a repeated measures MANOVA framework with effect size f=.11 (a small effect size equivalent to Cohen's d=.22), alpha=.05, adequate statistical power=.80, and 4 measurement time points, with a small natural correlation among repeated measures of r=.15, a total sample of 196 participants would be needed for adequate power to detect multivariate significance. This sample would generate adequate (.80) power to detect effects as small as d=.17, or less than a fifth of a standard deviation from clinical cutoffs, in the safety analyses of Hypothesis 2b. Therefore, we propose to recruit a total sample of **200 evaluable participants in the late puberty cohort** to ensure adequate statistical power to test the two hypotheses of Aim 2 and to conduct the exploratory analysis of Aim 3.

C8. Expected Outcomes

Aim 1: Findings will determine that the treatment practice of blocking puberty in gender dysphoric youth is not only tolerable and safe, but that this practice improves the mental health of these youth by avoiding the development of secondary sex characteristics that are undesirable. We anticipate that bone density during puberty suppression will continue to accrue at a pre-pubertal rate. Collectively, these outcomes will help clinicians and caregivers make the critical decision to move forward with treatment of gender dysphoric youth. Additionally, policy makers will have expanded scientific evidence that will support the medical necessity of this treatment approach, informing policies related to gender transition.

Aim 2: In our late pubertal cohort, findings will determine that gender transition with cross-sex hormones is tolerable, safe, and improves the mental health of transgender adolescents. Additionally, cross-sex hormone treatment may lead to a decrease in high-risk behavior including sexual activity and drug use. Collectively, these outcomes will help clinicians and caregivers provide the necessary early care for transgender adolescents. Rigorous scientific evidence supporting the benefits of early treatment will help reduce the anxiety often experienced by providers and caregivers that cross-sex hormones are harmful and the fear that the irreversible changes occurring from hormones is the wrong choice for the health and well being of their children and patients. Treatment models that are proven to improve mental health outcomes and decrease life-threatening behaviors are medically necessary and need to be unequivocally framed as such.

C9. Potential Problems and Alternative Strategies

A first potential problem with the study is participant attrition between baseline enrollment and follow-up visits, which could impact the validity of results and the power to detect relationships among variables. Older adolescents are migratory by nature, although continued hormone treatment is a compelling reason to stay engaged in care. In our pilot study of transgender youth at CHLA, attrition over one year was 15%. We are over-recruiting by 20% in the late pubertal cohort to account for potential increased attrition over 2 years. For

the youth in the early pubertal cohort, we anticipate that attrition rates will be lower than in the older cohort based on clinical observation and on increased parental involvement. We are over-recruiting in this cohort by 10% to allow for potential participant attrition.

Collecting and transmitting data consistently across four participating sites can be challenging. Data must be cleaned and stored uniformly in order to perform useful analyses and generate meaningful conclusions. Therefore, we have budgeted for a data coordination core staff at CHLA, whose responsibility it is to conduct trainings of data collection personnel at each site concerning appropriate procedures for recruitment, enrollment, and use of computer assisted data collection. Additionally, core staff will be responsible for verifying that data from all sites are comparable.

While this study will likely cause minimal risk to participants, they could potentially experience distress and/or triggering of negative feelings when asked questions on the ACASI of a more sensitive nature. If patients experience discomfort or distress, as outlined in the Protection of Human Subjects attachment, they will be directed immediately to onsite mental health providers for evaluation and counseling.

[Finally, a study design that had a more scientifically robust control arm was considered, but in light of both the WPATH and the Endocrine Society's guidelines we decided against such an approach as we deemed it both unfeasible and not ethically responsive to the population served.]

C10. Benchmarks of Success and Timeline

Benchmarks (see **Timeline of Project Activities** in the Budget Justification section) include: 1) The successful completion of project protocols and human subject approvals; 2) development and piloting of the ACASI instrument; 3) standardized training of project coordinators and data collection staff; 4) successful enactment of recruitment protocols; 5) completion of baseline collection of bone density, physiologic, and psychosocial date; 6) data collection at each follow-up point; 7) data management and analysis; and 8) published manuscripts and dissemination.

C11. Dissemination

The PIs from all sites will each attend one national conference per year to disseminate findings beginning in Year 2. Data obtained from this study are of interest to and will be presented to participants at gender specific conferences such as the World Professional Association of Transgender Health, Gender Odyssey, Philadelphia TransHealth Conference, and Gender Spectrum, and also at national conferences concerning the health of children and adolescents such as the American Academy of Pediatrics, Society for Adolescent Health and Medicine, Pediatric Academic Societies, and others. Beginning in Year 3, peer-reviewed publications will be developed pertaining to cross-sectional hypotheses and research questions found in Aims 1 and 2, though the bulk of publications are longitudinal in nature and will be developed in Year 5. Dissemination of findings to State and County officials, policy makers, and organizations will begin in Year 3, when preliminary data become available.

C12. Future Directions

The development of this network of investigators is an essential step in the progress to eradicating the health disparity that currently exists for transgender youth. Together, these sites anticipate expanding investigation into the experiences and needs of transgender youth from early childhood through early adulthood. Our network of four research sites views the proposed research as only the beginning of a larger body of longitudinal outcome research needed for understanding and optimizing medical interventions for gender non-conforming children and adolescents. A distinct strength of the proposed network is that we will be well-suited to address new and unanticipated issues as they arise within the context of the proposed work in order to refine aspects of future studies. As children and adolescents who are blocked in puberty move on to cross-sex hormones, it will be critical to understand the impact of GnRH analogues on their bone mineral density, as well as neurocognitive development. We plan to extend our investigations to include the youngest cohort of gender non-conforming children in order to identify resiliency factors, understand the role of social support systems, and identify predictors of persistence of gender non-conformity from childhood into adolescence. Additionally, future investigation into the experience of parenting gender non-conforming and transgender youth is of interest and importance. This proposal sets up an ideal framework to continue collecting longitudinal data from the cohorts recruited for this initial work as well as understand the additional complexities of this population.

PROTECTION OF HUMAN SUBJECTS

Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

Transgender children and adolescents, those who experience incongruence between assigned birth sex and internal gender identity, are a poorly understood and distinctly understudied population in the United States. The limited available data suggest that transgender youth who are gender dysphoric (persistently distressed about their gender incongruence) are at increased risk for numerous health disparities in comparison to their peers, including higher rates of anxiety, depression, suicide, and substance use. The development of undesired secondary sex characteristics during puberty intensifies the distress associated with gender incongruence and increases the risk for these conditions. Current clinical practice guidelines include strategies for treating transgender youth with the use of: 1) gonadotropin releasing hormone (GnRH) agonists to suppress endogenous puberty in early pubertal adolescents in order to avoid the development of undesired secondary sex characteristics and 2) cross sex hormones to induce masculine or feminine features in late pubertal adolescents. The goal of these interventions is to decrease gender dysphoria and ameliorate other potential negative health outcomes. These guidelines are used at academic and community-based centers across the U.S.; however, they are only partially empirically derived and based on very limited data, largely from non-U.S. sources. Further, there are no data available examining the physiologic and metabolic consequences of these treatments in adolescents. This represents an obvious gap in the literature that has significant implications for clinical practice across the U.S. The general lack of U.S. data leaves healthcare providers uncertain about optimal care for these highly vulnerable youth. This proposed research will fill gaps in knowledge, provide empirical evidence to inform clinical care, and would be the first study of its kind evaluating longitudinal outcomes of medical treatment for multi-ethnic, transgender youth in the U.S.

The proposed research study will collect data from 328 transgender youth (88 early pubertal [Tanner stages 2 and 3] and 240 late pubertal youth [Tanner stages 4 and 5]) and 88 parents of the early pubertal group in order to evaluate the impact of hormone therapy.

Potential participants will be receiving services at one of the four sites (Boston, Chicago, Los Angeles, and San Francisco) and seeking hormonal intervention to either delay the progression of puberty through the use of GnRH agonists or begin phenotypic gender transition by adding cross-sex hormones. Recruitment will be conducted by one of the care providers at the site, and ongoing retention will be supported through the participants receiving transgender care services.

Inclusion criteria for early pubertal cohort includes the presence of gender dysphoria, expressed anxiety about endogenous puberty and/or the development of undesired secondary sexual characteristics, Tanner stage 2 or 3 of sexual development, and a desire to undergo puberty suppression. Patients and parents/legal guardians must be able to read and understand English. To be eligible for enrollment, the participants cannot have utilized GnRH agonists or hormones prior to the initial visit.

Inclusion criteria for the late pubertal cohort includes transgender youth between 13 and 21 years of age with gender dysphoria, Tanner stage 4 or 5 of sexual development, and an interest in pursuing a phenotypic gender change with cross-sex hormones. Patients must be able to read and understand English. To be eligible for enrollment, the participants cannot have utilized cross sex hormones prior to the initial visit.

The involvement of children is required as this study focuses on transgender youth who are either early pubertal or late pubertal. The hormonal interventions are ideally utilized in Tanner stages 2 and 3 for puberty delay or Tanner stages 4 and 5 for phenotypic gender change. No other special vulnerable populations will be enrolled.

Physiologic, psychosocial, behavioral, and medical data will be collected at the baseline visit (T0), 6 months (T1), 12 months (T2), and 24 months (T3). The timeline for data collection is correlated with expected standard of care clinical visits so as to not overly burden the participants or their parents/legal guardians with additional

study visits. Physiologic data will be abstracted from medical records, while demographic, psychosocial, and behavioral data will be collected via Audio Computer-Assisted Self-Interviewing (ACASI) technology.

The research is being conducted at Children's Hospital Los Angeles, University of California San Francisco Benioff Children's Hospital, Lurie Children's Hospital of Chicago, and Boston Children's Hospital in order to investigate the impact of the treatment on multi-ethnic transgender youth in the United States. These four academic hospitals situated strategically across the country have dedicated transgender youth clinics and are considered the national leaders in the care of transgender children and adolescents. All four sites employ a similar model for care that includes medical and mental health professionals and represent some of the most experienced providers in the country doing this work.

ACASI data collected at the collaborating sites will be encrypted and transferred to CHLA. Upon transfer of the encrypted data to CHLA, the data will be stored on CHLA's secured network (with firewall protection), which cannot be accessed by anyone outside of CHLA. All case report forms (CRFs) will be entered into password protected databases at the site and be transmitted securely with an ID core to CHLA. A password will be used to access survey data and chart abstraction files and will be made accessible only to the Principal Investigators and study staff. These data will be archived in a password-protected database on the local network on a daily basis. The data coordination staff, housed at CHLA, will support all PIs with the generation of a cross-site protocol for data collection and templates for the Institutional Review Boards at each site. Study-wide data management procedures, including integration and verification of multi-site data, will take place at CHLA.

b. Sources of Materials

Case report forms (CRFs) for abstracting physiological parameters (height, weight, BMI, sitting height, Tanner stage), hormone levels, and bone health from medical chart data will be used.

Data will be collected directly from participants and for the early pubertal group, their parents/legal guardians, via ACASI to minimize concerns about confidentiality. Demographic data for the early pubertal group collected will include age, ethnicity, educational level and birth city/country, as well as data specific to the transgender population, such as age of realization of transgender status, age of first living in the desired gender role, and domains where they are living in their desired gender role, if any. Demographic, mental health, and behavioral data will also be collected from the parents of the youth in the early pubertal group.

Demographic data for the late pubertal group collected will include age, ethnicity, educational level, and birth city/country, as well as data specific to the transgender population, such as age of realization of transgender status, age of first transitioning or "real life experience" in the desired gender role, prior sexual activity, sexual orientation, previous hormone use, and length of treatment. Psychosocial indicators from the late pubertal group include gender dysphoria, quality of life, body esteem, depression, suicidal ideation, drug use, sex work, and high-risk sexual behavior.

Only site-specific research staff and local institution IRB personnel conducting quality assurance activities will have access to individually identifiable private information about the participants.

No personal identifying information (e.g., name, tracking information, etc.) will be placed on any of the CRFs or collected within the ACASI survey. All study-specific records will be identified by a coded number only, to maintain confidentiality. Only the research staff will have access to the database linking the participant's unique ID code and name in a secure network, password-protected file or in a secure location under double-lock when not in use and with restricted access during work hours and/or when unattended.

Anthropometric measures, hormone levels, laboratory result data, and bone health will be abstracted by trained, research staff and recorded on CRFs. All CRFs will be entered into password protected databases at the site and transmitted securely with an ID to CHLA.

For the ACASI baseline and follow-up surveys each participant will be assigned a code and their pre- and post-surveys will be linked via this code. A master list of the codes assigned to participants will be kept in a secure,

password protected file at each site or in a secured location under double-lock when not in use and with restricted access during work hours and/or when unattended.

c. Potential Risks

The risks of participation in this study are minimal and are not greater than those that would be accepted by other persons not participating in the study. Participants are expected to be exposed only to minimal risk based on questions asked and the confidential system of data collection. While all safeguards will be in place to protect their identity, there is also potential risk that identifying information collected could be accessed by someone other than the research team. A number of precautions and safeguards have been developed in order to protect the confidentiality of individuals who participate in the study. No personal identifying information will be used on the CRFs or ACASIs. Consent forms will be filed and stored separate from the raw data in a secured location under double-lock when not in use and with restricted access during work hours and/or when unattended.

As this is an observational study, there are no alternative treatments or procedures.

Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Site care members will recruit participants for the study by speaking with patients and their parents/legal guardians face-to-face or by telephone. Information regarding the study will be provided and interest in participation will be assessed.

If the potential participants are interested in enrolling in the study, staff members from Children's Hospital Los Angeles, Boston Children's Hospital, Lurie Children's Hospital of Chicago, and University of California at San Francisco who have received IRB certification will consent participants. The Institutional Review Boards at all sites requires that all research participants review and sign an informed consent/permission/assent form or be given an information sheet (if a waiver of written consent is obtained). The informed consent/permission/assent form covers information about the overall purpose of the study, what the study entails, potential risks, potential benefits to participating individuals and society, the confidentiality of data, and contact information for the Principal Investigator and the IRB. Once informed consent/permission/assent has been obtained, the research staff will have the form reviewed by a fellow research team member, who will confirm that it is fully completed before it is filed in a secure location under double-lock when not in use and with restricted access during work hours and/or when unattended.

For participants aged 7 to 13 years old, the participant will sign an age-appropriate assent form, and the parent/legal guardian will sign a consent/permission/assent form.

For participants aged 14 to 17 years old, the participant and the parent/legal guardian will sign a consent/permission/assent form.

For participants aged 18 years or older, the participant will sign a consent/permission/assent form.

Project Staff will inform participants that they have the right to skip any survey questions that make them feel uncomfortable. Participants will be informed that participation is completely voluntary and that they are free to stop their involvement in the study at any time without any negative consequences. They will be informed of their rights to privacy and confidentiality and will be told that their answers to the survey will be kept confidential and not shared with others outside of the research staff. They will be informed that no information about them or provided by them during the research will be disclosed to others without their written permission, except if necessary to protect their rights or welfare (for example, if they are injured and need emergency care) or if required by law (i.e., child or elder abuse, harm to self or others, or reports of certain infectious diseases).

Participation in all phases of the data collection process is voluntary. There will be no mandatory participation through any venue (e.g., court-ordered, condition of probation, compliance with agreement to work, or to

maintain housing). The consent/permission/assent form clearly states that participation is voluntary and that a decision to not participate is entirely up to each individual.

b. Protections Against Risk
A number of precautions and safeguards have been developed in order to protect the confidentiality of individuals who participate in the study.

No personal identifying information (e.g., names) of the participants will appear in any computer files associated with this research project in any location. Participants will be assigned a unique identification number code. A key file that matches the ID number to the participant and organization will be maintained in a secure data repository within the project offices at each of the four sites. Data will be kept strictly confidential, except as required by law, and stored on a secure network, with password protection such that only authorized users will have access to the file server. All computers will be located in locked facilities, and consent forms will be filed and stored separate from the raw data in a secured location under double-lock when not in use and with restricted access during work hours and/or when unattended. Any temporary data files kept on removable storage devices, as well as printouts derived from data analysis, will be stored in a locked compartment when not in use.

After a subject completes the ACASI survey at a site, the ACASI data will be secured by being saved in a password-protected compressed file. As each section of the survey is completed, the section will be saved and encrypted so that no one is able to look at previous screens to view the data. If the subject completing the interview requires a short break, it is possible to stop the interview and return later to complete it. Only authorized users with a login name and password will be able to open the survey on the laptop.

Data will remain on the CHLA server during data collection, verification, cleaning, and analysis. At the closure of the study, electronic and hardcopy data will be maintained for a minimum of six years per CHLA IRB policy. The local site data will be retained at the local site for the length of time as defined the local site's IRB policy. Project binders at CHLA containing archival information will be stored a minimum of six years and will then be eligible to be destroyed.

The research staff and protocol will be certified through the local IRB at each of the four sites to conduct research on human subjects, especially as related to children. This observational study is 46.404, research not involving greater than minimal risk, and 46.408 requirements for permission by parents or guardians and for assent by children will be followed. Within the first two months of funding, the project staff will submit an application to the IRB for protocol approval. Throughout the project, staff will continue to work with IRB at their respective sites to protect the rights and confidentiality of all individuals who participate in data collection.

As this is an observational study, adverse events are not anticipated. However, there is some risk that answering questions about some of the topics may be uncomfortable or upsetting. In the event of discomfort or upset, there are medical and psychological professionals on the research team who can provide ongoing support as needed. Participants do not have to answer any question in the computerized interview that they do not want to answer. Furthermore, participants will be informed that at any point, they may stop if they do not wish to continue the questionnaire. In the event of an adverse event, it will be reported to the IRB as per protocol to ensure the safety of participants.

Potential Benefits of the Proposed Research to Human Subjects and Others

While there are no potential direct benefits to the research participants, the risks involved in this study are minimal and the anticipated societal benefits outweigh them.

Importance of the Knowledge to be Gained

As described above the risks involved in this study are minimal and the anticipated societal benefits outweigh them. The proposed research provides the opportunity to obtain a better understanding of transgender youth, improve their care, and share information on a local and national level about how to provide care and hormone

therapy for gender dysphoric children and adolescents. The information that is learned from this project will support innovative approaches to identifying, understanding, and providing optimal care for early pubertal and late pubertal, multi-ethnic transgender youth.

Data and Safety Monitoring Plan

Not applicable as the proposed research does not include a clinical trial.

ClinicalTrials.gov Requirements

Not applicable as the proposed research does not include a clinical trial.

INCLUSION OF WOMEN AND MINORITIES

Inclusion of Women

As a study of transgender children and youth, those designated at birth as female or male and who identify with a gender that is inconsistent with that label will be eligible to be enrolled in this study. These individuals will be recruited to participate in the proposed study as the target population and may identify with any number of gender identity labels including, but not limited to transgender, female, transgender female, male, and transgender male.

Inclusion of Minorities

All racial and ethnic categories are eligible for our proposed study; however, our proposed sample will be predominantly White, Hispanic, and African American. This reflects the target populations of transgender individuals that are currently being served within the four sites. The inclusion criteria include monolingual Spanish speakers, and the ACASI instruments and consents will be made available in Spanish.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: The Impact of Early Medical Treatment in Transgender Youth

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	(b)(4); (b)(6)				
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American					
White					
More than One Race					
Total					

Study 1 of 1

Funding Opportunity Number: PA-12-111. Received Date: 2014-11-05T18:44:21.000-05:00

INCLUSION OF CHILDREN

The proposed research will include coded data from early and late pubertal, gender dysphoric children and adolescents (Tanner stages 2-5) to understand the impact of hormone therapy to suppress puberty. Data will be collected from their medical charts as well as audio computer-assisted self-interviewing surveys; however, all data collection will be coded to help ensure confidentiality. Children and adolescents will be asked to complete surveys at baseline, 6 months, 12 months, and 24 months. As described in the Research Plan, the Principal Investigator, research staff, and collaborating partners have a long history of working with and conducting research related to transgender children and adolescents.

MULTIPLE PI/PD LEADERSHIP PLAN

Johanna Olson, M.D., Norman Spack, M.D., Robert Garofalo M.D., M.P.H., and Stephen Rosenthal, M.D., will serve as a team of Principal Investigators on this application, each responsible and accountable to the National Institutes of Health (NIH) for the proper conduct of the research. The rationale for the decision to act as a multiple PI team is based on the fact that these four investigators bring unique experiences and knowledge that will integrate and complement one another in the implementation of this project. Additionally, the involvement of these four sites provides larger numbers than a single site could of potential participants for a research endeavor seeking to understand an uncommon experience. The PIs serve as the Medical Directors of four university-affiliated programs in the United States currently providing care for transgender youth.

Dr. Johanna Olson, M.D. (Pediatrics and Adolescent Medicine), is the Medical Director of the Center for Transyouth Health and Development at Children's Hospital Los Angeles (University of Southern California). She and her team based at CHLA, including Co-Is Marvin Belzer, M.D., Leslie Clark, Ph.D., M.P.H., and Sheree Schrager, Ph.D., M.S., lead the largest transgender youth program in the United States. The combined expertise of this team provides both comprehensive clinical knowledge and extensive research expertise in the area of transgender adolescents. Patients seek care at this center from as far away as Shanghai. While we acknowledge that Dr. Olson, the lead PI, is still early in her career, she is surrounded by an experienced team of mentors at her own site and at the three other sites participating in the proposed project. Dr. Belzer has extensive experience managing clinical trials, including his participation as a site PI in the NICHD supported REACH and ATN Networks for the past 20 years as well as the PACTG/IMPAACT Network for 15 years. Dr. Belzer will serve as the primary mentor for Dr. Olson, a role he has had for the past four years. Drs. Clark and Schrager bring an extensive portfolio of skills including the design and implementation of behavioral interventions, expertise in research methodology and statistical analysis, and prior experience managing multi-site studies.

Dr. Norman Spack, M.D. (Pediatric Endocrinology), and his team, including Co-I Psychologist Amy Tishelman, Ph.D., are principals in Boston Children's Hospital's Gender Management Service (GeMS) which opened in 2007. GeMS was the first pediatric academic program in the western hemisphere to treat pubescent teens. Dr. Spack treated 200 transgender adults from 1985-2006, and in 2004, GeMS' personnel were trained by the Amsterdam team and given their protocols for psychometric assessment and pubertal suppression. 75% of GeMS' patients come from a 150 mile radius of Boston; the rest come from throughout the US. His Co-Investigator, Amy Tishelman, Ph.D., is a clinical psychologist with significant expertise in scholarship and clinical realms; before joining the GeMS team she was the Director of Child Protection Clinical Services at Boston Children's Hospital and subsequently Director of Training and Research for that program. She has decades of experience evaluating children and families and is a recognized expert in the area of trauma and interpersonal violence with an interest in helping vulnerable children and adolescents.

Dr. Robert Garofalo, M.D., M.P.H. (Pediatrics and Adolescent Medicine), is Co-Director of the Gender and Sex Development Program, Division Head of Adolescent Medicine at Lurie Children's Hospital of Chicago, and Associate Professor of Pediatrics at Northwestern University's Feinberg School of Medicine. He will serve as the PI for the Chicago site. He and his team, including Co-Is Marco Hidalgo, Ph.D., Lisa Simons, M.D., Courtney Finlayson, M.D., and Scott Leibowitz, M.D., and Ethicist Joel Frader, M.D., bring a wealth of expertise caring for and conducting research in adolescent populations, with particular focus on transgender and other sexual minority youth. The Chicago team has been providing clinical services to gender non-conforming youth for more than a decade. Their multidisciplinary program for gender non-conforming youth and transgender youth undergoing medical suppression of puberty or initiating cross-sex hormone therapy brings together experts in pediatrics/adolescent care, endocrinology, psychology and child development, psychiatry, surgical subspecialties, and medical ethics. The team has extensive experience conducting NIH-funded multisite clinical and behavioral research with marginalized populations of youth.

Dr. Stephen M. Rosenthal, M.D. (Pediatric Endocrinology), Professor of Pediatrics, Program Director for Pediatric Endocrinology, Co-Director of the Disorders of Sex Development Clinic, and Medical Director of the Child and Adolescent Gender Center (CAGC) at the University of California San Francisco (UCSF) Benioff Children's Hospital, is an established clinical investigator with greater than 30 years of experience in child and adolescent endocrinology. He will serve as PI for the UCSF site. His Co-Investigator, Diane Ehrensaft, Ph.D.,

and Mental Health Director of the UCSF CAGC, is an internationally recognized child psychologist/gender specialist. His Co-Investigator, David Glidden, Ph.D., Professor of Epidemiology and Biostatistics at UCSF, brings extensive expertise in research design and statistical analysis. The UCSF CAGC has been providing multi-disciplinary care for gender non-conforming/transgender youth and adolescents for the past six years. The UCSF CAGC is the only such multi-disciplinary gender program in Northern California and attracts patients not only from California, but from as far away as Florida and Egypt.

Primary Roles and Areas of Responsibility for Each PI

- Administrative
  - Upon successful funding, the award will be made to Children's Hospital Los Angeles (CHLA). All participants will be enrolled at one of the four study sites – The Center for Transyouth Health and Development (CHLA), The Child and Adolescent Gender Center (University of California San Francisco), The Gender, Sexuality and HIV Prevention Center (Lurie Children's Hospital of Chicago), or the Gender Management Service (Boston Children's Hospital). Drs. Olson, Garofalo, Rosenthal, and Spack will work collaboratively to prepare reports and other requirements for submission to the NIH. Each will oversee the administrative responsibilities at each of their respective institutions.
- Technical
  - Dr. Olson, given her experience conducting the pilot studies that serve as the principal preliminary data for the current application, will work with Drs. Rosenthal, Spack, and Garofalo to finalize study implementation protocols at each site, so that each site carries out the project in the same manner. Data will be collected systematically, with identical operating procedures including CRFs, ACASI programming, and data flow sheets to facilitate the creation of a data repository that is suitable for analysis and available for all four sites to explore. The data will be owned equally by each of the four participating sites.
  - Dr. Olson will oversee the protocols for data collection, including physiologic and psychosocial at each site.
  - All four PIs will finalize protocols for each cohort in the study and standardize these to ensure that there is consistency in delivery across the four study sites.
  - All four PIs, with the project directors/Co-Is at each site, will direct recruitment, retention, data collection, and intervention delivery, with support from the project team at each of their respective sites. Data will be stored at all sites and safely transferred via secure protocols to CHLA for cleaning and merging.
  - Drs. Clark and Schrager will direct data management, including integration and verification at CHLA.
  - Drs. Clark, Schrager, and Glidden will direct data analysis at CHLA and UCSF.
  - Dr. Garofalo will be involved in scientific direction and support data interpretation and dissemination.

Governance/Structure

- Communication plan
  - These four sites are positioned across the U.S., necessitating ongoing communication via teleconference. The investigators have budgeted for a one-week training at the beginning of the study, in which all of the teams will meet at one of the principal sites. The investigators have also budgeted travel for mid-study team meetings that will allow the research team to review study progress and ensure successful completion. In the final year, the investigators have budgeted travel for the purpose of meeting around data analysis, interpretation, and manuscript writing.
  - During the accelerated start up phase of the study, the PIs and Co-Is will meet twice weekly via Skype/phone with the project managers at each site to discuss scientific issues, intervention sessions, recruitment, implementation, etc. Additional meetings will be scheduled with members of the study team as needed.
  - Decisions on scientific direction will be made during the weekly meetings. Dr. Olson will make final decisions on the delivery of the intervention protocol, whereas Drs. Clark and Schrager will make final decisions regarding instruments, data collection tools, and the statistical analyses for manuscript preparation.

- Procedures for resolving conflicts – The four sites have determined that the following domains may require third party arbitration in the event of conflict that is not resolved through discussion amongst the sites:
    - Authorship dispute – issues of conflict will be heard by an objective observer from the WPATH executive board.
    - Scientific dispute – scientific conflict will be arbitrated by a pediatric endocrinologist faculty member at Children's Hospital of Pennsylvania.
    - Safety – a data safety monitoring board will be established by the end of month three to provide periodic assessment of the protocol and preliminary results, and assist with conflict arising from potential safety issues.
- Distribution of resources to four sites – CHLA will be the primary institution for the receipt of the award and the three other sites will be supported through subcontracts from CHLA. Primary responsibility for administration at the CHLA site is Dr. Marvin Belzer, along with financial administrator Priscilla Brown. This team has extensive experience with financial administration of multiple site projects.

Dissemination

- In order to share process and outcome data from this project with the broader scientific community, abstracts will be submitted for presentation to at least one scientific conference per year. Conferences where data may be presented include annual meetings of the Society for Adolescent Health and Medicine, The American Academy of Pediatrics, The World Professional Association of Transgender Health, Pediatric Academic Societies, The Endocrine Society, The American Public Health Association, The American Psychological Association, The American Psychiatric Association, and others. Manuscripts are planned on the following topics:
    - Description of the sample and preliminary results
    - Description of the intervention
    - Primary outcomes

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CONSORTIUM/CONTRACTUAL ARRANGEMENTS

PA-12-111 Research on the Health of LGBTI Populations (R01)
Due Date: November 5, 2014
Earliest Start Date if funded: July 1, 2015
Duration of Project Period: Five years
Project Title: The Impact of Early Treatment in Transgender Youth
Primary Applicant: Children's Hospital Los Angeles
Principal Investigator: Johanna Olson

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreements consistent with that policy.

Programmatic Arrangement:

Children's Hospital Los Angeles
Children's Hospital Los Angeles (CHLA) will be the primary institution for the receipt of the award and the three partner sites will be supported through subcontracts from Children's Hospital Los Angeles. CHLA will act as the data center or core for the project, and the CHLA research team led by Johanna Olson, MD, will have the primary responsibility for creating data protocols in partnership with the other sites. Programming of the ACASI, creation of CRFs, and data management, cleaning, and analysis will occur at CHLA.

Boston Children's Hospital
The Site Principal Investigator, Norman Spack, MD, will implement the proposed observational study on the impact of providing treatment to early-pubertal and late-pubertal transgender youth. Dr. Spack will take primary responsibility for the implementation of the scientific aims of this project at Boston Children's Hospital and will collaborate in the dissemination of findings. The key personnel at Boston Children's Hospital will collaborate with the partner sites to submit abstracts for presentation at scientific conferences and in co-authorship of publications to disseminate important research findings as a result of this study.

Lurie's Children's Hospital of Chicago
The Site Principal Investigator, Robert Garofalo, MD, will take primary responsibility for the implementation of the scientific aims of this project at Lurie Children's Hospital of Chicago. The Co-Investigators will share responsibility for the scientific and fiscal integrity of the project, assist in protocol development, and examine ethical aspects of the implementation of clinical guidelines and issues surrounding school or voluntary organization exclusion or other discrimination based on gender nonconformity.

University of California San Francisco
The Site Principal Investigator, Stephen M. Rosenthal, MD, will implement the proposed observational study on the impact of providing treatment to early-pubertal and late-pubertal transgender youth. Dr. Rosenthal will take primary responsibility for the implementation of the scientific aims of this project at Benioff Children's Hospital at UCSF and will collaborate in the dissemination of findings. The key personnel at UCSF will collaborate with the partner sites to submit abstracts for presentation at scientific conferences and in co-authorship of publications to disseminate important research findings as a result of this study.

Fiscal Arrangement:

Children's Hospital Los Angeles: includes full project costs (CHLA site costs, consortium site costs, and CHLA's and consortium sites' F&A)

	Direct	Indirect ((b)(4)%)	TOTAL Per Year
Year 1	$	$	$
Year 2	$	$	$
Year 3	$ (b)(4)	$ (b)(4)	$ (b)(4)
Year 4	$	$	$
Year 5	$	$	$
TOTAL	**$**	**$**	**$**

Boston Children's Hospital:

	Direct	Indirect ((b)(4)%)	TOTAL Per Year
Year 1	$	$	$
Year 2	$	$	$
Year 3	$ (b)(4)	$ (b)(4)	$ (b)(4)
Year 4	$	$	$
Year 5	$	$	$
TOTAL	**$**	**$**	**$**

Lurie Children's Hospital of Chicago:

	Direct	Indirect ((b)(4)%)	TOTAL Per Year
Year 1	$	$	$
Year 2	$	$	$
Year 3	$ (b)(4)	$ (b)(4)	$ (b)(4)
Year 4	$	$	$
Year 5	$	$	$
TOTAL	**$**	**$**	**$**

University of California San Francisco:

	Direct	Indirect ((b)(4)%)	TOTAL Per Year
Year 1	$	$	$
Year 2	$	$	$
Year 3	$ (b)(4)	$ (b)(4)	$ (b)(4)
Year 4	$	$	$
Year 5	$	$	$
TOTAL	**$**	**$**	**$**

Ann & Robert H. Lurie
Children's Hospital of Chicago™
Gender and Sex Development Program

Robert Garofalo, MD, MPH
Division Chief, Adolescent Medicine
Director, Center for Gender, Sexuality and HIV Prevention
Ann & Robert H. Lurie Children's Hospital of Chicago
255 East Chicago Avenue, Box 161
Chicago, Illinois 60611-2991

October 29, 2014

Johanna Olson, MD, MPH
Assistant Professor of Clinical Pediatrics
Medical Director, Center for Transyouth Health and Development
Children's Hospital Los Angeles
5000 W. Sunset Blvd., 4th Floor
Los Angeles, CA 90027

Dear Dr. Olson:
We are delighted to join your team of investigators for the project entitled "Impact of Early Treatment on Transgender Youth" to be submitted through the R01 mechanism. We have a great deal of experience in working with transgender children and adolescents at the Center for Gender, Sexuality and HIV Prevention at Lurie Children's Hospital of Chicago. Specifically, we have focused on the collection of data, both behavioral and clinical biomarkers, in marginalized populations and the translation of this data into intervention development. I was Committee Member on the Institute of Medicine (IOM) Study on The Health of Lesbian, Gay, Bisexual and Transgender People that established as a research priority the need for longitudinal outcomes research on medical interventions for transgender people. As such, it is a distinct honor to be part of this collaborative network of research teams and investigators.
For this proposal, the following key personnel will work with you to implement an observational study of the impact of providing early treatment to peri-pubertal and post-pubertal transgender youth.

Rob Garofalo, M.D., MPH, Site Principal Investigator, will take primary responsibility for the implementation of the scientific aims of this project at Lurie Children's as well as collaborate to disseminate findings.

Lisa Simons, M.D., Co-Investigator, Pediatrician, will share responsibility for patient care as a Pediatrician and the scientific and fiscal integrity of this project and will oversee all research activities at Lurie Children's. She will also share responsibility for data analysis and dissemination of findings with Dr. Garofalo.

Marco A. Hidalgo, Ph.D., Co-Investigator, will supervise the Project Coordinator in her/his management of day-to-day tasks by coordinating IRB submissions, developing and overseeing effective recruitment strategies and providing ongoing advice regarding confidential data collection/ management procedures. He will also assist the Data Manager in refining assessment instruments, managing study databases, and creating data manuals.

Scott Leibowitz, MD., Co-Investigator/Psychiatrist, will assist in protocol development as well as conduct patient assessments at the Lurie site.

Ann & Robert H. Lurie
Children's Hospital of Chicago
Gender and Sex Development Program

Joel Frader, M.D., Ethicist, will examine ethical aspects of the implementation of clinical guidelines, including: the age and developmental/maturational characteristics of decision-making capacity of children and adolescents for treatment; the ways in which clinicians and parents manage different points of view regarding treatment, particularly when parent perspectives are based on particular religious and philosophical convictions; and ethical and legal issues surrounding school or voluntary organization exclusion or other discrimination based on gender nonconformity. Dr. Frader will also assist in protocol development.

Courtney Finlayson, M.D., Co-Investigator/Endocrinologist, will be the lead Endocrinologist at the Lurie site and will: conduct patient assessments; review laboratory results; consult with the study teams on all endocrinological issues such as bone development and growth. Dr. Finlayson will also assist in protocol development.

The key personnel at Lurie Children's Hospital will collaborate with the partner sites to submit abstracts for presentation at scientific conferences and in co-authorship of publications to disseminate important research findings as a result of this study.

In addition, along with your Division Head, Dr. Belzer, I will help co-mentor you as the contact PI as I/we have done throughout your young and promising career. Although as contact PI you may be relatively inexperienced with NIH-funded multisite clinical trials, it is my opinion that you are the emerging clinical and research leader in this field. As you are aware the proposed network of 4 sites gave very careful consideration in deciding the contact PI for this proposal. I have full confidence that with the appropriate guidance and mentoring that you are ideally suited to lead this effort. You have my full support and I am happy to provide whatever mentorship is required to make this project a success.

Lastly, reflecting back upon the recommendations of the IOM, the proposed body of research is not only innovative but of considerable public health significance as it will have a profound impact on the body of clinical evidence. This evidence is sorely needed to hone the safety and efficacy of clinical guidelines and to properly advise parents and families on proposer treatment options for their gender non-conforming and transgender children and adolescents. We look forward to doing this work as a Team Investigators from across the U.S. and in partnership with the NIH/NICHD.

Sincerely,

Rob Garofalo, MD, MPH
Co-Director of the Gender and Sex Development Program
Division Head of Adolescent Medicine, Lurie Children's Hospital
Professor of Pediatrics and Preventive Medicine
Northwestern University's Feinberg School of Medicine

Boston Children's Hospital
Department of Medicine
Division of Endocrinology
Senior Associate in Medicine

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Associate Clinical Professor of Pediatrics

Norman Spack, M.D.,
Boston Children's Hospital
Department of Endocrinology
Co-Director, Gender Management Service
333 Longwood Avenue
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October 16th, 2014

Johanna Olson, MD, MPH
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Medical Director, Center for Transyouth Health and Development
Children's Hospital Los Angeles
5000 W. Sunset Blvd., 4th Floor
Los Angeles, CA 90027

Dear Dr. Olson:

We are delighted to join your team of investigators for the project entitled "Impact of Early Treatment on Transgender Youth" to be submitted through the R01 mechanism. We have a great deal of experience in working with transgender children and adolescents at the Gender Management Service (GeMS) at Boston Children's Hospital and Harvard Medical School. Specifically, we are the first clinic to treat transgender and gender questioning youth in North America, and have years of experience working with this population and an investment facilitating research to enhance the well-being of these youth and facilitate optimal clinical care. Some of the attributes of the children and adolescents we treat and our approaches have been recently described in papers published in the journals *Pediatrics* (Spack et al, 2012), and Professional Psychology: Research and Practice (Tishelman et al, in press) and we believe that the research proposed in this study is timely and will have a significant impact on clinical care.

For this proposal, the following key personnel will work with you to implement an observational study of the impact of providing early treatment to peri-pubertal and post-pubertal transgender youth.

Norman Spack, M.D, Site Principal Investigator, will take primary responsibility for the implementation of the scientific aims of this project at Boston Children's Hospital, as well as collaborate to disseminate findings.

Amy Tishelman, Ph.D., Co-Investigator, and Director of Clinical Research for the DSD-GeMS program, will share responsibility for the scientific and fiscal integrity of this project and will oversee research activities at Boston Children's Hospital. Along with Dr. Shumer, she will hire, train and supervise the Project Coordinator and other staff. She will assist in data collection, protocol development, and intervention implementation plans. She will collaborate in data analysis, interpretation, preparation of manuscripts, and dissemination activities. Dr. Tishelman, a Clinical Psychologist, will also provide therapeutic services and urgent assessments related to research participation.

Daniel Shumer, M.D.., Co-Investigator and endocrinologist, will share responsibility for the scientific and fiscal integrity of this project and, along with Dr. Tishelman, will help to oversee research activities at Boston Children's Hospital. He will work with Dr. Tishelman to hire, train and supervise the Project Coordinator and other staff and assist in data collection, protocol development, and intervention implementation plans. As an endocrinologist, he will help to conduct patient assessments; review laboratory results; consult with the study teams on all endocrinological issues such as bone development and growth. He will collaborate in data analysis, interpretation, preparation of manuscripts, and dissemination activities.

Sincerely,

Norman Spack, M.D.
Co-Director, Gender Management Service
Endocrine Division, Boston Children's Hospital
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Stephen M. Rosenthal, MD
Professor of Pediatrics
Program Director, Pediatric Endocrinology
Medical Director, Child and Adolescent Gender Center
University of California San Francisco, Benioff Children's Hospital

October 24, 2014

Johanna Olson, MD, MPH
Assistant Professor of Clinical Pediatrics
Medical Director, Center for Transyouth Health and Development
Children's Hospital Los Angeles
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Los Angeles, CA 90027

Dear Dr. Olson:

We are delighted to join your team of investigators for the project entitled "Impact of Early Treatment on Transgender Youth" in response to PA-12-111, to be submitted through the R01 mechanism. We have a great deal of experience working with transgender children and adolescents at the Child and Adolescent Gender Center (CAGC) at the University of California San Francisco (UCSF) Benioff Children's Hospital. The UCSF CAGC is one of the leading centers for the multidisciplinary care of transgender youth in the U.S., and serves as the Pediatric/Adolescent clinical arm of the widely recognized UCSF Transgender Center of Excellence. Our CAGC investigators have authored numerous publications on transgender youth, including a recently in-press "State-of-the-Art" invited review in *Pediatrics* and an in-press invited review in the "Approach-to-the-Patient" series in the *Journal of Clinical Endocrinology and Metabolism.* I am currently serving as the official representative of the Pediatric Endocrine Society to the Endocrine Society's Clinical Practice Guidelines Revision Task Force for the Care of Transgender individuals. In addition, as a basic and clinical investigator with > 30 years' experience in child and adolescent endocrinology, I have had significant experience conducting multi-center trials, and am currently serving as UCSF Site Principal Investigator for NIH/NICHD "Disorders of Sex Development: Platform for Basic and Translational Research". Our UCSF CAGC team strongly believes that the research proposed in this study is timely and will have a significant impact on clinical care.

For this proposal, the following key personnel will work with you to implement an observational study of the impact of providing early treatment to early-pubertal and late-pubertal transgender youth:

Stephen M. Rosenthal, M.D., Site Principal Investigator, will take primary responsibility for the implementation of the scientific aims of this project at UCSF Benioff Children's Hospital, as well as collaborate to disseminate findings.

Diane Ehrensaft, Ph.D., Co-Investigator, will share responsibility for the scientific and fiscal integrity of this project. As a Clinical Psychologist, Dr. Ehrensaft will assist in protocol development, data collection, data analysis, preparation of manuscripts, and dissemination of findings at scientific meetings. She will also assist Dr. Rosenthal with IRB submissions, and will assist in developing and overseeing effective recruitment strategies.

David V. Glidden, Ph.D., Co-Investigator and Biostatistician, will work closely with Dr. Schrager at Children's Hospital Los Angeles, and will provide advice and support on analytic approaches. Dr. Glidden will contribute expertise on the statistical design of the study and will focus on analysis of the metabolic data in this project. He will be responsible for the design, analysis plan, and execution of these analyses.

As you know, existing clinical practice guidelines for the multidisciplinary care of transgender youth and adolescents are primarily based on expert opinion, as only minimal outcomes data currently exist. Our collaborative proposal has the potential to provide such needed outcomes data to inform appropriate care for a population of youth that has been marginalized and poorly understood. We are deeply committed to this work and seeing it reach its fruition.

Sincerely,

Stephen M. Rosenthal

Stephen M. Rosenthal, MD
Professor of Pediatrics
Program Director, Pediatric Endocrinology,
Medical Director, Child and Adolescent Gender Center
University of California San Francisco, Benioff Children's Hospital

RESOURCE SHARING PLAN: DATA SHARING PLAN

The proposed research will include final data from approximately 240 transgender youth in the late pubertal group, 88 youth in the early pubertal group, and 88 parents/legal guardians of the early pubertal group. The final datasets will include self-reported demographic and behavioral data from surveys with the subjects and laboratory data from specimens provided for routine care of transgender youth. The dataset for the early pubertal group will also include demographic, behavioral, and mental health data about the youth from the parent. Although the final dataset will be stripped of identifiers prior to release for sharing, we believe that there remains the possibility of deductive disclosure of subjects with unusual characteristics. Thus, we will make the data and associated documentation available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

We wish to make our results available to the transgender community, mental and medical health providers, public health practitioners, and scientists interested in studying, providing, and receiving competent mental and medical healthcare. Thus, we will make our data available to other NIH investigators under the data-sharing agreement after a reasonable time period that includes enough opportunity to prepare and have submitted for publication four manuscripts presenting the basic outcomes of the project. Our plan also includes sharing of study findings through multiple presentations at meetings of both community oriented audiences (such as the World Professional Organization of Transgender Health and GLAMA) and national pediatric and transgender health conferences (such as the American Academy of Pediatrics, the Society for Adolescent Health and Medicine, the Pediatric Endocrine Society, and the Endocrine Society).