A. COVER PAGE

Project Title: The Impact of Early Medical Treatment in Transgender Youth	
Grant Number: 5R01HD082554-09	**Project/Grant Period:** 08/01/2015 - 07/31/2025
Reporting Period: 02/01/2024 - 07/31/2025	**Requested Budget Period:** 02/01/2024 - 07/31/2025
Report Term Frequency: Final	**Date Submitted:** 01/06/2026
Program Director/Principal Investigator Information: JOHANNA L OLSONKENNEDY , MD MS BS MS **Phone Number:** (b)(6) **Email:** jolson@chla.usc.edu	**Recipient Organization:** CHILDREN'S HOSPITAL OF LOS ANGELES 4650 Sunset Boulevard Mailstop #97 LOS ANGELES, CA 900276062 **UEI:** DVL1CMRMWRN9 **EIN:** 1956121916A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: (b)(6)	**Signing Official:** (b)(6)
Human Subjects: Yes **HS Exempt:** NA **Exemption Number:** **Phase III Clinical Trial:** NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

The primary objective of this observational, longitudinal, multicenter study is to extend the initial 2-year follow-up period to evaluate physiological and psychological effects of gonadotropin releasing hormone analogs (GnRHa) and gender affirming hormones (GAH) on participants for an additional 4 years. The second objective is to enhance the diversity and size of existing cohorts by enrolling additional youth of color into both cohorts and enroll additional assigned male at birth youth into the GAH cohort. The third objective is to add measurements of psychosocial variables required to answer new questions posed by longer term follow-up. As reported in the 2023 RPPR, the revised aims are as follows. Aim 1: Evaluate the longer-term physiological and psychosocial impact of GnRHa initiated in early puberty on youth with gender dysphoria by extending follow-up for an additional 4 years (3, 4, 5 and 6 years after initiation of puberty blockers). Aim 1a: Examine the trajectories of height, weight, and bone mineralization as youth continue treatment with pubertal suppression and initiate treatment with gender-affirming hormones. Aim 1b: Continue assessment of mental health and psychosocial well-being with the existing measures and with the addition of new measures as these children progress from preteen to adolescent development. Aim 1c: Enroll youth with a focus on enrolling ethnic/racial minority youth to better reflect the increasingly diverse clinical populations. Aim 2: Evaluate the longer-term physiological and psychosocial impact of GAH (estrogen or testosterone) in later puberty in youth with gender dysphoria by extending follow-up for an additional 4 years (3, 4, 5 and 6 years after initiation of gender affirming hormones). Aim 2a: Evaluate longer-term effects of sex steroids on cardiovascular risk factors such as obesity, blood pressure, and lipids. Aim 2b: Employ a developmental framework to assess mental health and psychosocial well-being with the existing measures and with the addition of new measures as youth move into later adolescence and early adulthood. Aim 2c: Enroll youth and young adults with a focus on enrolling ethnic/racial minority youth and young adults to better reflect the increasingly diverse clinical populations. Aim 3: Compare effects of gender-affirming hormones within and outside the context of prior pubertal suppression. Many within GnRHa cohort will begin GAH for induction of masculinization or feminization over time. In addition, a subset of GAH cohort was receiving GnRHa at enrollment. These two sets together can be considered a GnRHa + GAH group. We propose to longitudinally examine across 2–3-year follow-up this GnRHa + GAH group with age- and sex assigned at birth- matched GAH only group to compare psychosocial well-being between GAH youth with and without a history of GnRHa use. Exploratory Aim 4: Characterize emerging sub-cohorts. Examination of emerging sub-groups from the first five years will inform optimal care models for the increasing diversity of youth with gender dysphoria. We propose to explore the demographics, challenges, and medical needs of non-binary youth (i.e., youth who identify outside of a male/female binary) as well as those youth who discontinue GnRHa or GAH. Exploratory Aim 5: Continue to collect data beyond 6 years following initiation of GnRHa or GAH from all cohorts and conduct ongoing analyses to report on these findings.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File Uploaded : TYC 2024 Accomplishments.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File Uploaded : TYC 2024 Opportunities for Training & Professional Development.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

In support of re-engagement and retention and honoring the importance of providing study results to study participants, a third newsletter/infographic was sent to study participants that shared study findings and publications. It focused on disseminating the 2-year follow-up data shared in the Chen et al. article "Psychosocial Functioning in Transgender Youth after 2 Years of Hormones" published in the New England Journal of Medicine.

During 2024, the MPIs and Co-Is conducted the following presentations.
Invited Presentations
Chen, D. (2024, May). Examining the evidence for pediatric gender-affirming care. Invited presentation for the University of Chicago's Diversity & Activism Seminar Series for psychology trainees. Chicago, IL. [Virtual meeting].
Chen, D. (2024, June). Psychological functioning in transgender and nonbinary youth after 2-years of hormone treatment. Invited presentation at the Promoting Mental Health for Sexual and Gender Minority Youth: Evidence-Based Developmental Perspectives Workshop sponsored by the National Institute of Mental Health. [Virtual presentation].
Chen, D. (2024, October). Examining the evidence base for gender affirmative care for transgender youth. Invited Grand Rounds Speaker and Visiting Professor, Weill Cornell Department of Pediatrics. New York, NY.
Chen, D. (2024, November). Psychological outcomes of gender-affirming hormone treatment. Invited presentation at the annual meeting of the European Society of Paediatric Endocrinology. Liverpool, UK.
Chen, D. (2024, December). Examining the evidence base for gender affirmative care for transgender youth. Invited presentation for the Psychiatry and Behavioral Sciences Women's Board Grand Rounds at RUSH University Medical Center. Chicago, IL.
Garofalo, R (2024, October). Controversies in the Standards of Care for Transgender Youth: The Growing Evidence and Questions that Remain in Pediatric Gender Care. Mount Sinai Medical Center, New York, NY.
Garofalo, R (2024, January). The TYC-US Study and the State of the Science of Pediatric Gender Affirming Care in the United States. University of Bristol Law School, Bristol, United Kingdom
Olson-Kennedy, J. (2024). Results to Date from the Trans Youth Care Study. Children's Hospital Los Angeles Science Dinner Night. Children's Hospital Los Angeles, Los Angeles, CA.
Olson-Kennedy, J. (2024). Results to Date from the Trans Youth Care Study. Division of Adolescent and Young Adult Medicine Grand Rounds. Children's Hospital Los Angeles, Los Angeles, CA.
Rosenthal, S. (2024, March 14). Advances and Challenges in the Care of Transgender/ Gender Diverse Youth. Argentina Pediatric Endocrine Regional Meeting, Buenos Aires, Argentina.
Rosenthal, S. (2024, October 23). Advances and Challenges in the Care of Transgender/ Gender Diverse Youth. Foundation for Advanced Education in the Sciences (FAES), Virtual Endocrinology Review Course, in conjunction with the National Institutes of Health, Bethesda, MD.
Rosenthal, S. (2024, October 30). Advances and Challenges in the Care of Transgender/ Gender Diverse Youth. Virtual Lecture). Israel Pediatric Endocrinology Conference, Tel Aviv, Israel.
Rosenthal, S. (2024, November 1). Advances and Challenges in the Care of Transgender/ Gender Diverse Youth: An Endocrinologist's View. Minnesota Multicultural Summit (Virtual), Minnesota Psychological Association, Minneapolis, MN.

Conference Presentations
Chen, D., Berona, J., Coyne, C.A., Chan, Y.M., Ehrensaft, D., Hidalgo, M.A., Olson-Kennedy, J., Radix, A., Rosenthal, S.M., & Garofalo, R. (2024, March). Predictors of diverse mental health trajectories following 4 years of treatment with gender-affirming hormones. Platform research presentation at the Society for Adolescent Health Annual Meeting, San Diego, CA.
Chen, D., Kuper, L., Olson, K., Arnoldussen, M., & van der Meulen, I. (2024, September). New long-term research on adolescent gender-affirming medical care. Symposium presentation at the biennial meeting of the World Professional Association for Transgender Health, Lisbon, Portugal.
Huit, T.Z., Whitehead, J., Chan, Y.M., Ehrensaft, D., Garofalo, R., Hidalgo, M.A., Olson-Kennedy, J., Rosenthal, S.M., Tishelman, A.C., & Chen, D. (2024, September). Longitudinal analysis of aggression and irritability following initiation of testosterone therapy in transgender and gender diverse adolescents and young adult. Oral presentation at the biennial meeting of the World Professional Association for Transgender Health, Lisbon, Portugal.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

B.2 (TYC 2024 Accomplishments.pdf)

B.2. Accomplishments

Major Activities

Major activities that were accomplished during the grant year include:

- Completed Year 4 data collection; cleaned data; conducted/conducting analyses
- Will complete Year 5 data collection by 12/31/24
- Continued to enroll new participants to diversify the cohorts
- Publication of a manuscript titled “Laboratory Changes During Gender-affirming Hormone Therapy in Transgender Adolescents” documenting that abnormal laboratory results are rare in transgender and gender diverse adolescents prescribed gender-affirming hormone therapy and, if present, occur within six months of gender-affirming hormone therapy initiation – please see below under Key Outcomes and C.1 Publications
- Acceptance of two manuscripts titled “Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy” and “Physical Activity Among Youth Receiving Gender-Affirming Treatment in the United States”– please see below under Key Outcomes and C.1 Publications
- Conducting analyses and developing manuscripts on the following. We anticipate these will be submitted for peer-review during the next project year.
  - Unpublished; (b)(4)
- Conducted quarterly scientific web conferences
- Utilized $75,000 in endowment funding from Private Source; (b)(4) Private Source: to support biostatistician time to guide analysis of study data

Specific Objectives

Study objectives during this past year were focused on activities to:

- Conduct baseline, months 6 and 12, and years 5-8 study visits with participants
- Recruit new study participants to diversify the cohorts
- Retain study participants
- Analyze data as identified by the PIs and Co-Is to explore data findings related to 2-year and further outcomes and develop key manuscripts

Since reopening recruitment to new participants to further diversify the study population, we have recruited 13 GnRHa participants and their parent or caregiver and 79 gender-affirming hormone participants. The percentage of youth participants who had a male sex designated at birth was 62% in the GnRHa cohort and 70% in the gender-affirming hormone cohort. In addition, the percentage of non-Latine White participants was 54% in the GnRHa cohort and 38% in the gender-affirming hormone cohort. We will continue to engage with youth and their parent/caregiver to increase enrollment and diversification of participants in the study.

We have completed all study visits through year 4 with the original GnRHa and GAH cohorts. For year 5, there is one GnRHa visit and one GAH visit that are remaining. Study participant re-engagement and retention has

been a key activity in meeting study objectives especially considering the impact of COVID-19 on study activities as evidenced by the 36- and 48-month retention percentages in Table 1. The retention percentages are increasing as participants have re-engaged in the study and are completing annual visits. Our Year 5 retention, which has almost been completed, is 78% with the original GnRHa cohort and 70% in the original GAH cohort. It should be noted that many of the original GAH cohort participants are now in their early twenties, and retention of these participants as they complete high school, go to college, start working, and become independent of their parents is challenging. The strong efforts of our study coordinators to build rapport with these young adults has led to the retention of older participants in the study, and we expect this trend to continue throughout the next year.

Table 1: Youth/Young Adult Participant Retention and Percentage of Visits Completed for Original Cohort and New Enrollment Cohort

	GnRHa Participants		GAH Participants	
Visit	**Retention %***	**% of Visits Completed**	**Retention %***	**% of Visits Completed**
6-month	**85%**	**92%**	**92%**	**92%**
12-month	**76%**	**88%**	**80%**	**87%**
18-month	**71%**	**86%**	**70%**	**78%**
24-month	**71%**	**86%**	**76%**	**77%**
36-month**	**46%**	**79%**	**20%**	**73%**
48-month**	**70%**	**77%**	**54%**	**73%**
60-month***	**78%**	**75%**	**70%**	**73%**
72-month	**68%**	**67%**	**69%**	**68%**
84-month	**81%**	**29%**	**76%**	**43%**
96-month	**100%**	**6%**	**100%**	**6%**

***Denominator for retention (expected visits) does not include participants who withdrew consent, passed away, or have not reached the end of their extended follow-up window.**
****36- and 48-month visits for the original cohort were impacted by COVID.**
*****Only 1 visit left each for the GnRHa and GAH original cohorts at this time point.**

Significant Results, Key Outcomes, or Other Achievements

The study team conducted data analyses of the data through 2 years of follow-up with the following results and outcomes.

In “Laboratory Changes During Gender-affirming Hormone Therapy in Transgender Adolescents”, data were analyzed for 293 transgender and gender diverse (TGD) participants (68% designated female at birth) with no previous history of gonadotropin-releasing hormone analog use. Hemoglobin and hematocrit decreased in adolescents prescribed estradiol (-1.4 mg/dL and -3.6%, respectively) and increased in adolescents prescribed testosterone (+1.0 mg/dL and +3.9%) by 6 months after gender-affirming hormone therapy (GAHT) initiation. Thirteen (6.5%) participants prescribed testosterone had hematocrit > 50% during GAHT. There were no differences in hemoglobin A1c, alanine transaminase, or aspartate aminotransferase. There was a small increase in prolactin after 6 months of estradiol therapy in transfeminine adolescents. Hyperkalemia in transfeminine adolescents taking spironolactone was infrequent and transient if present. Analyses demonstrated that abnormal laboratory results are rare in TGD adolescents prescribed GAHT and, if present, occur within 6 months of GAHT initiation. Future guidelines may not require routine screening of these laboratory parameters beyond 6 months of GAHT in otherwise healthy TGD adolescents.

In “Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy” the study team reported that over the 24-month observation period, participants starting gender-affirming hormone

therapy demonstrated significant improvements in appearance congruence, psychological well-being, social satisfaction and self-efficacy and significant reductions in negative affect and negative social perception. Significant associations between appearance congruence and different indicators of emotional functioning were observed at baseline and over time.

Physical activity of participants in the GnRHa cohort was described in “Physical Activity Among Youth Receiving Gender-Affirming Treatment in the United States”. The analysis found that physical activity (as assessed by the Physical Activity Questionnaire - child version) was lower than that historically reported for cisgender youth, and there were no significant changes over 24 months of treatment with puberty blockers. In addition, participants who were designated male at birth had lower physical activity scores than those designated female at birth, and transgender and gender diverse children who were older at baseline had lower physical activity than those who had started pubertal blockade at younger ages.

B.4. What opportunities for training and professional development has the project provided?

(b)(6)

Under the guidance of study staff at Children's Hospital Los Angeles, (b)(6) (b)(6) created a newsletter/infographic that focused on disseminating the 2-year follow-up data shared in the Chen et al. article “Psychosocial Functioning in Transgender Youth after 2 Years of Hormones” published in the New England Journal of Medicine. The creation of the newsletter provided the trainees with the opportunity to learn how to translate scientific data and writing into language and a format that is accessible and understandable to young adults and their families. The iterative process included reading the article and understanding the contents, working with a publishing program to visualize the data, meeting with a youth community advisory board for input and feedback, and obtaining the primary author’s and IRB’s approval of the final newsletter.

At Ann & Robert H. Lurie Children’s Hospital of Chicago, the Trans Youth Care study has provided professional development opportunities for junior faculty and psychology postdoctoral fellows working under Dr. Chen’s supervision. With respect to junior faculty mentoring, Johnny Berona, PhD, was successfully awarded a Northwestern University Feinberg School of Medicine KL2 under the mentorship of Dr. Chen that leverages TYC data. Specifically, Dr. Berona is examining suicide risk in the TYC sample in the 4 years following gender-affirming hormone initiation. In addition, (b)(6) (b)(6) collaborated with Dr. Chen in their presentation at the 2024 Society for Adolescent Health and Medicine focused on 4-year trajectories of internalizing and externalizing symptomology in the TYC cohort, and (b)(6) (b)(6) collaborated with Dr. Chen in developing a manuscript (currently under review at (b)(4); Unpublished (b)(4); Unpublished

With respect of postdoctoral fellow mentoring, (b)(6) (b)(6) to extend this work and recruit a small sample of youth initiating testosterone and examine change in these constructs (i.e., anger, irritability, aggression) in the acute 3-month initiation/titration phase in a short-term longitudinal study.

At Benioff Children’s Hospital, UCSF, the Trans Youth Care study has provided continued professional development opportunities for junior faculty under Dr. Rosenthal’s supervision. Specifically, Janet Lee, MD, MPH, MAS, is analyzing skeletal health in the TYC cohort that enrolled in the study at initiation of pubertal suppression and subsequently transitioned with gender-affirming hormones. In addition, Dr. Lee was recently awarded a K-23 grant from the NICHD/NIH focused on skeletal effects of pubertal suppression followed by peer-concordant puberty in transgender and gender diverse youth.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Olson-Kennedy J, Wang L, Wong CF, Chen D, Ehrensaft D, Hidalgo MA, Tishelman AC, Chan YM, Garofalo R, Radix AE, Rosenthal SM. Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2025 January 16;77(1):41-50. PubMed PMID: 39818652; PubMed Central PMCID: PMC12170176; DOI: 10.1016/j.jadohealth.2024.11.014.
Complete	Olson-Kennedy J, Wang L, Wong CF, Chen D, Ehrensaft D, Hidalgo MA, Tishelman AC, Chan YM, Garofalo R, Radix AE, Rosenthal SM. Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2025 July;77(1):41-50. PubMed PMID: 39818652; PubMed Central PMCID: PMC12170176; DOI: 10.1016/j.jadohealth.2024.11.014.
Complete	Olson-Kennedy J, Wang L, Wong CF, Chen D, Ehrensaft D, Hidalgo MA, Tishelman AC, Chan YM, Garofalo R, Radix AE, Rosenthal SM. Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2025 July;77(1):41-50. PubMed PMID: 39818652; PubMed Central PMCID: PMC12170176; DOI: 10.1016/j.jadohealth.2024.11.014.
Complete	Olson-Kennedy J, Wang L, Wong CF, Chen D, Ehrensaft D, Hidalgo MA, Tishelman AC, Chan YM, Garofalo R, Radix AE, Rosenthal SM. Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2025 July;77(1):41-50. PubMed PMID: 39818652; PubMed Central PMCID: PMC12170176; DOI: 10.1016/j.jadohealth.2024.11.014.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

C.5.a Other Products

NOTHING TO REPORT

C.5.b Resource Sharing

Progress implementing the resource sharing plan:

NOTHING TO REPORT

C.5.c Data Management and Sharing

Not Applicable

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	Sr/Key	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6); eRA Commons User Name	Y	Chan, Yee-Ming	BS,PHD,MD	PD/PI	(b)(4); (b)(6); EFFORT					NA
	Y	Garofalo, Robert	BS,MPH,MD	PD/PI						NA
	Y	Olson-Kennedy, Johanna L	BS,MS,MS,MD	PD/PI						NA
	Y	ROSENTHAL, STEPHEN M	BA,MD	PD/PI						NA
	Y	Chen, Diane		Co-Investigator						NA
	N	(b)(6)		Co-Investigator						NA
	N		MPH	Data Manager						NA
	N			Research Coordinator						NA
	N			Research Coordinator						NA
	N			Research Coordinator						NA
	N			Research Coordinator						NA
	N			Research Coordinator						NA
	N		MPH	Research Manager						NA

Glossary of acronyms:
Sr/Key - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND NOTICE OF FUNDING OPPORTUNITIES REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

Sub-Project ID	Study ID	Study Title	Delayed Onset	Clinical Trial	NCT	NIH-Defined Phase 3	ACT
	324174	The Impact of Early Medical Treatment in Transgender Youth	NO	NO			NO

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

Section 1 - Basic Information (Study 324174)

1.1. Study Title *

The Impact of Early Medical Treatment in Transgender Youth

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

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

1.4. Clinical Trial Questionnaire *

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

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

Section 2 - Study Population Characteristics (Study 324174)

2.1. Conditions or Focus of Study

- Gender Dysphoria

2.2. Eligibility Criteria

GnRHa YOUTH COHORT
Inclusion Criteria
- Presence of gender dysphoria as determined by a clinician;
- Tanner stage 2, 3, or 4 of sexual development
- Appropriate to undergo puberty suppression with GnRH agonists;
- Ages 8 through 16 years inclusive;
- Ability to read and understand English;
- Receiving or planning to receive services at a study site clinic; and
- Willing and able to provide informed assent.

Exclusion Criteria
- Prior utilization of GnRH agonists;
- Precocious puberty (natal males younger than 9 years or natal females younger than 8 years);
- Pre-existing osteoporosis;
- Presence of serious psychiatric symptoms (e.g., active hallucinations, thought disorder) that would impair the individual's ability to provide true informed consent or participate in the baseline survey;
- Visibly distraught (e.g., suicidal, homicidal, exhibiting violent behavior) at the time of consent or the baseline survey; or Intoxicated or under the influence of alcohol or other substances to such an extent that in the opinion of the study staff, the ability to give true informed consent or to understand and answer the questions is impaired.

GnRHa PARENT/CAREGIVER COHORT
Inclusion Criteria
- Parent or caregiver of a child who meets the GnRHa Youth Cohort inclusion/exclusion criteria;
- Ages 18 and above;
- Ability to read and understand English; and
- Willing and able to provide signed informed consent.

Exclusion Criteria
- Presence of serious psychiatric symptoms (e.g., active hallucinations, thought disorder) that would impair the individual's ability to provide true informed consent or participate in the baseline survey;
- Visibly distraught (e.g., suicidal, homicidal, exhibiting violent behavior) at the time of consent or the baseline survey; or
- Intoxicated or under the influence of alcohol or other substances to such an extent that in the opinion of the study staff, the ability to give true informed consent or to understand and answer the questions is impaired.

GENDER-AFFIRMING HORMONE COHORT
Inclusion Criteria
- The presence for gender dysphoria as determined by a clinician;
- Appropriate for initiating phenotypic gender change with gender-affirming hormones;
- Ages 12 through 20 years inclusive;
- Ability to read and understand English;
- Receiving or planning to receive services at a study clinic; and
- Willing and able to provide signed informed consent or assent.

Exclusion Criteria
- Prior utilization of gender-affirming hormones;
- Previously or currently enrolled in the GnRHa cohort;
- Presence of serious psychiatric symptoms (e.g., active hallucinations, thought disorder) that would impair the individual's ability to provide true informed consent or participate in the baseline survey;
- Visibly distraught (e.g., suicidal, homicidal, exhibiting violent behavior) at the time of consent or the baseline survey; or
- Intoxicated or under the influence of alcohol or other substances to such an extent that in the opinion of the study staff, the ability to give true informed consent or to understand and answer the questions is impaired.

2.3. Age Limits	Min Age: 8 Years	Max Age: N/A (No limit)
2.3.a. Inclusion of Individuals Across the Lifespan		
2.4. Inclusion of Women and Minorities	Inclusion_of_Women_Minorities_and_Children.pdf	
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Plan.pdf	
2.6. Recruitment Status	Enrolling by invitation	

2.7. Study Timeline	Study_Timeline.pdf
2.8. Enrollment of First Participant (SEE SECTION 6.3)	

INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

Inclusion of Women and Minorities

This project meets standards for inclusion of women and minorities.

As a study of transgender children, youth, and young adults, potential participants who identify with a gender that is incongruent with the sex they were designated at birth may be eligible to be enrolled in this study. These individuals will be recruited to participate in the proposed study and may identify with any number of gender identity labels including, but not limited to transgender, gender fluid, nonbinary, genderqueer, female, transgender female, male, and transgender male. The goal of the study is to have equal numbers of designated male at birth and designated female at birth participants in the cohorts. Currently, the gender identity percentages are relatively similar within the GnRHa cohort with 42.6% identifying as transmasculine; 47.9% transfeminine; and 9.6% nonbinary, genderqueer, or gender fluid (48% assigned female at birth and 52% assigned male at birth). However, within the gender-affirming hormone cohort, the participants are 60.3% transmasculine; 33.7% transfeminine; 6% nonbinary, genderqueer, or gender fluid (65% assigned female at birth and 35% assigned male at birth).

Initially, all racial and ethnic categories were eligible to enroll in the study during the first grant period; however, it became evident that the percentage of white youth enrolling in the study was higher than expected, reflecting the rates of youth in care at all four of the sites. To address the lack of racial/ethnic diversity, the MPIs decided at the protocol team meeting in late 2018 to restrict new transmasculine participant enrollments in the gender-affirming hormone cohort to participants of color, with an emphasis on non-Hispanic/Latinx youth. In 2022, when it was determined to be possible to reopen enrollment to new participants, the MPIs decided that recruitment would focus on – but would not necessarily be restricted to – transmasculine youth of color and transfeminine youth of any race/ethnicity in the gender-affirming cohort, and on both transmasculine and transfeminine youth of color in the GnRHa cohort. In our current cohorts, the gender-affirming hormone youth cohort is 67% white, 16% Hispanic/Latinx, 4% black/African American, 3% Asian, and 10% more than one race or ethnicity. The GnRHa youth cohort is 67% white, 9% Hispanic/Latinx, 4% black/African American, 3% Asian, and 17% other or more than one race or ethnicity.

Inclusion of Children

This project meets standards for inclusion of children.

The research conducted thus far and during the renewal grant period will include coded data from early and late pubertal gender dysphoric children, adolescents, and young adults to understand the impact of hormone therapy to suppress puberty and assist in phenotypic transition. In the initial grant period, youth participants have ranged in age from 8 to 20, with a mean age of 11 years in the GnRHa cohort and 16 years in the gender-affirming hormone cohort at enrollment. Data will be collected from their medical charts as well as surveys and interviews; however, all data collection will be coded to help ensure confidentiality. Children and adolescents will be asked to complete surveys at baseline and every six months through the month-24 visit and annually thereafter for seven years. As described in the Research Plan, the Principal Investigator, research staff, and collaborating partners have a long history of providing care for and conducting research with transgender children and adolescents.

Parent/Caregiver participants must be at least 18 years of age; this is required due to self-consent requirements for participating in the study. It is not expected that we would have a potential participant under age 18 as the minimum age for the youth participants is 8 years.

The investigative team of MPIs and Co-Is has extensive expertise in providing medical and psychosocial care to children, adolescents, and young adults. The four study sites are children's hospitals with strong academic partnerships. The research space in the four children's hospital sites is age-appropriate, and the facilities are ideal for conducting research with children. Most of the members of the PI and Co-I teams are active clinicians in addition to their research endeavors as university faculty.

Involvement of children in this study will be in compliance with all applicable subparts of 45 CFR 46, Subpart D – Additional Protections for Children Involved as Subjects in Research, as well as other pertinent Federal and State laws/regulations.

RECRUITMENT AND RETENTION PLAN

Recruitment is conducted through the clinics at the four study sites as inclusion criteria require that participants access care at the study site in order for the study to obtain observational data on the medical impact of a GnRHa to prevent progression beyond early puberty or gender-affirming hormones for phenotypic transition. In addition, these four clinic sites are some of the largest providers of transgender pediatric care in the country.

During the original grant period, our team noted that the diversity of the enrolled study population needed to be improved. This led to the launching of a selective recruitment strategy specifically to increase participation of youth of color with an emphasis on non-Hispanic/Latinx youth in the GnRHa cohort. In the gender-affirming hormone (GAH) cohort, the same emphasis was placed on transmasculine participant recruitment; however, due to the smaller number of transfeminine participants in the GAH cohort, a focus on youth of color was not implemented. During the tenure of the first grant period, UCSF opened a second site at Benioff Children's Hospital Oakland that began providing gender care for that geographic region and is located in a more ethnically diverse neighborhood. Recruitment from this site, in addition to selective recruitment at the other sites, has provided additional diversity to the study population. In order to assist with identifying additional recruitment strategies, Dr. Asa Radix has joined the protocol team as a co-investigator. In addition, Dr. Olson-Kennedy at Children's Hospital Los Angeles obtained CTSI funding and IRB approval to conduct qualitative focus groups with transgender and gender diverse young adults of color to gather data about the challenges youth of color face in accessing care. The first three focus groups have been conducted, and funding has been sought to support additional focus groups. These strategies form the backbone of recruitment efforts to diversify the study population. In May 2023, recruitment opened for new participants, with a focus on recruiting youth of color.

The transition of the study visits from in-person to remote visits due to COVID-19 has supported retention as participants can complete the study visit in their own private space at a time that's convenient for them. If study participants prefer to complete their study visit in-person when they are at the clinic for their medical care, this is also available. We have found that some study participants prefer to have the in-person visit so that they can connect with the study coordinator.

We have completed all study visits through year 4 with the original GnRHa and GAH cohorts. For year 5, there is one GnRHa visit and one GAH visit that are remaining. Study participant re-engagement and retention has been a key activity in meeting study objectives especially considering the impact of COVID-19 on study activities as evidenced by the 36- and 48-month retention percentages in Table 1. The retention percentages are increasing as participants have re-engaged in the study and are completing annual visits. Our Year 5 retention, which has almost been completed, is 78% with the original GnRHa cohort and 70% in the original GAH cohort. It should be noted that many of the original GAH cohort participants are now in their early twenties, and retention of these participants as they complete high school, go to college, start working, and become independent of their parents is challenging. The strong efforts of our study coordinators to build rapport with these young adults has led to the retention of older participants in the study, and we expect this trend to continue throughout the next year.

Table 1: Youth/Young Adult Participant Retention and Percentage of Visits Completed for Original Cohort and New Enrollment Cohort

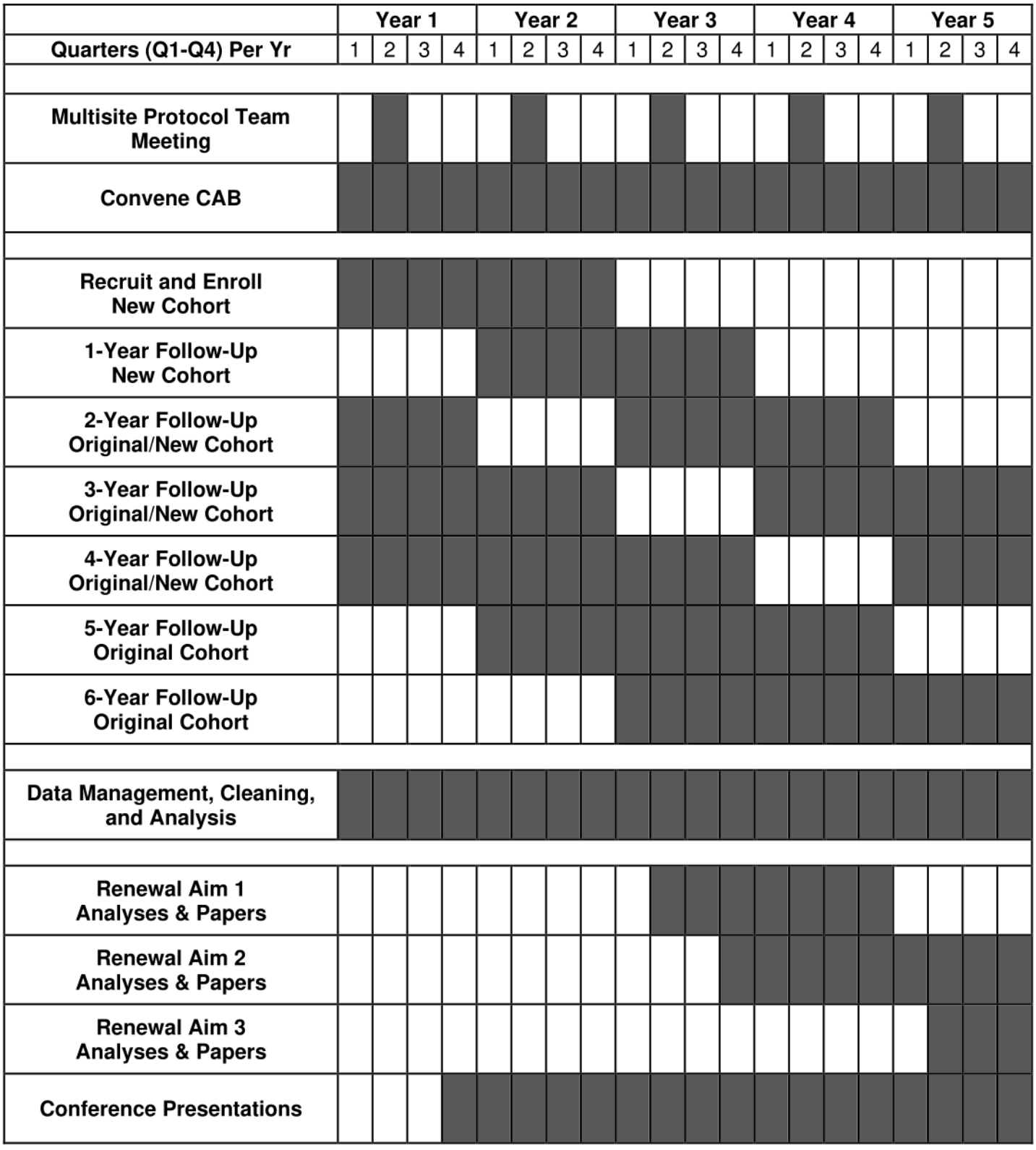
	GnRHa Participants		GAH Participants	
Visit	**Retention %***	**% of Visits Completed**	**Retention %***	**% of Visits Completed**
6-month	**85%**	**92%**	**92%**	**92%**
12-month	**76%**	**88%**	**80%**	**87%**
18-month	**71%**	**86%**	**70%**	**78%**
24-month	**71%**	**86%**	**76%**	**77%**
36-month**	**46%**	**79%**	**20%**	**73%**
48-month**	**70%**	**77%**	**54%**	**73%**
60-month***	**78%**	**75%**	**70%**	**73%**
72-month	**68%**	**67%**	**69%**	**68%**
84-month	**81%**	**29%**	**76%**	**43%**
96-month	**100%**	**6%**	**100%**	**6%**

***Denominator for retention (expected visits) does not include participants who withdrew consent, passed away, or have not reached the end of their extended follow-up window.**
****36- and 48-month visits for the original cohort were impacted by COVID.**
*****Only 1 visit left each for the GnRHa and GAH original cohorts at this time point.**

During the renewal grant period, retention efforts have been increased as study visits decrease in frequency to be annual rather than every six months after month 24. In addition, as some participants may be on gender-affirming hormones for three or more years, their medical care visits may also be further spaced apart. Study coordinators utilize retention strategies such as phone calls to participants, sending birthday cards, and providing small tokens of appreciation that will remind them of the study. As pediatric institutions, we recognize that some participants will age out of services during the nine-year extended follow-up period. To assist with retention, we have transitioned the survey to a web-based platform (REDCap) so that participants who no longer live close to the study site may be able to complete some study visits remotely. Also, we continue to retain these participants through strategies such as scheduling study visits during trips home from college. We update locator information at all visits, and we contact participants between study visits to correct and update contact information.

Retention will also be maintained through timely dissemination of data analysis to participants (youth and parents/caregivers) in a meaningful and digestible manner. In addition, presentations of study data are not limited to academic conferences and settings; we will continue to present at meetings that are attended by the community, which study participants and their family may be attending.

STUDY TIMELINE



2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 324152	Domestic	Ann & Robert H. Lurie Children's Hospital of Chicago Boston Children's Hospital Children's Hospital Los Angeles UCSF Benioff Children's Hospital Oakland UCSF Benioff Children's Hospital San Francisco
IER 324153	Domestic	Ann & Robert H. Lurie Children's Hospital of Chicago Boston Children's Hospital Children's Hospital Los Angeles UCSF Benioff Children's Hospital Oakland UCSF Benioff Children's Hospital San Francisco
IER 324154	Domestic	Ann & Robert H. Lurie Children's Hospital of Chicago Boston Children's Hospital Children's Hospital Los Angeles UCSF Benioff Children's Hospital Oakland UCSF Benioff Children's Hospital San Francisco

Inclusion Enrollment Report 324152

1. Inclusion Enrollment Report Title* : The Impact of Early Medical Treatment in Transgender Youth - 324152

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

3. Enrollment Location Type* : ● Domestic ○ Foreign

4. Enrollment Country(ies): USA: UNITED STATES

5. Enrollment Location(s): Ann & Robert H. Lurie Children's Hospital of Chicago
Boston Children's Hospital
Children's Hospital Los Angeles
UCSF Benioff Children's Hospital Oakland
UCSF Benioff Children's Hospital San Francisco

6. Comments: GnRHa (BLOCKER)YOUTH COHORT PLANNED AND CUMULATIVE ENROLLMENT
Cumulative (Actual) data below are for youth participants enrolled in the current study through 11/30/21 based on sex assigned at birth reported in the baseline visit.

Planned

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

Cumulative (Actual)

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

Inclusion Enrollment Report 324153

1. Inclusion Enrollment Report Title* : The Impact of Early Medical Treatment in Transgender Youth - 324153

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

3. Enrollment Location Type* : ● Domestic ○ Foreign

4. Enrollment Country(ies): USA: UNITED STATES

5. Enrollment Location(s): Ann & Robert H. Lurie Children's Hospital of Chicago
Boston Children's Hospital
Children's Hospital Los Angeles
UCSF Benioff Children's Hospital Oakland
UCSF Benioff Children's Hospital San Francisco

6. Comments: GnRHa (BLOCKER) PARENT/CAREGIVER COHORT PLANNED AND CUMULATIVE ENROLLMENT
Cumulative (Actual) data below are for parent/caregiver participants enrolled in the current study through 11/30/21 based on assigned sex at birth reported in the baseline visit.

Planned

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

Cumulative (Actual)

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

Inclusion Enrollment Report 324154

1. Inclusion Enrollment Report Title* :	The Impact of Early Medical Treatment in Transgender Youth - 324154
2. Using an Existing Dataset or Resource* :	● Yes ○ No
3. Enrollment Location Type* :	● Domestic ○ Foreign
4. Enrollment Country(ies):	USA: UNITED STATES
5. Enrollment Location(s):	Ann & Robert H. Lurie Children's Hospital of Chicago Boston Children's Hospital Children's Hospital Los Angeles UCSF Benioff Children's Hospital Oakland UCSF Benioff Children's Hospital San Francisco
6. Comments:	GENDER AFFIRMING HORMONE (GAH) COHORT PLANNED AND CUMULATIVE ENROLLMENT Cumulative (Actual) data below are for youth and young adult participants enrolled in the current study through 11/30/21 based on sex assigned at birth reported in the baseline visit.

Planned

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

Cumulative (Actual)

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

Section 3 - Protection and Monitoring Plans (Study 324174)

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

PROTECTION OF HUMAN SUBJECTS

Risks to Human Subjects
a. Human Subjects Involvement, Characteristics and Design

The primary objective of this observational, longitudinal, multicenter renewal study is to extend the initial 2-year follow-up period for an additional 4 years to evaluate the longer-term physiological and psychological impact of early medical treatment in two cohorts of dysphoric youth: 1) Those treated with puberty suppression initiated in early puberty who go on to receive gender-affirming hormones (estrogen or testosterone), and 2) those treated initially in later puberty with gender-affirming hormones. The sample of children, adolescents, and young adults will be recruited from patients presenting for care at any of the four sites along with one parent/primary caregiver for the children and youth accessing a GnRHa.

We will enroll up to 138 early pubertal youth participants in the GnRHa cohort (an additional 43 participants) who will meet the following inclusion and exclusion criteria:

Inclusion Criteria

- Presence of gender dysphoria as determined by a clinician
- Tanner stage 2, 3, or 4 of sexual development
- Appropriate to undergo puberty suppression with GnRH agonists
- Ages 8 through 16 years inclusive
- Ability to read and understand English
- Receiving or planning to receive services at a study site clinic and
- Willing and able to provide informed assent.

Exclusion Criteria

- Prior utilization of GnRH agonists
- Precocious puberty (natal males younger than 9 years or natal females younger than 8 years)
- Pre-existing osteoporosis
- Presence of serious psychiatric symptoms (e.g., active hallucinations, thought disorder) that would impair the individual's ability to provide true informed consent or participate in the baseline survey
- Visibly distraught (e.g., suicidal, homicidal, exhibiting violent behavior) at the time of consent or the baseline survey or
- Intoxicated or under the influence of alcohol or other substances to such an extent that in the opinion of the study staff, the ability to give true informed consent or to understand and answer the questions is impaired.

We will enroll as study participants up to 138 parents or caregivers (an additional 43 participants) of the early pubertal participants who will meet the following inclusion and exclusion criteria:

Inclusion Criteria

- Parent or caregiver of a child who meets the GnRHa Youth Cohort inclusion/exclusion criteria
- Ages 18 and above
- Ability to read and understand English and
- Willing and able to provide signed informed consent.

Exclusion Criteria

- Presence of serious psychiatric symptoms (e.g., active hallucinations, thought disorder) that would impair the individual's ability to provide true informed consent or participate in the baseline survey
- Visibly distraught (e.g., suicidal, homicidal, exhibiting violent behavior) at the time of consent or the baseline survey or
- Intoxicated or under the influence of alcohol or other substances to such an extent that in the opinion of the study staff, the ability to give true informed consent or to understand and answer the questions is impaired.

We will enroll up to 472 late pubertal cohort participants in the GAH cohort (an additional 156 participants) who will meet the following inclusion and exclusion criteria:

Inclusion Criteria

- The presence for gender dysphoria as determined by a clinician

- Appropriate for initiating phenotypic gender change with gender-affirming hormones
- Ages 12 through 20 years inclusive
- Ability to read and understand English
- Receiving or planning to receive services at a study clinic and
- Willing and able to provide signed informed consent or assent.

Exclusion Criteria

- Prior utilization of gender-affirming hormones
- Previously or currently enrolled in the GnRHa cohort
- Presence of serious psychiatric symptoms (e.g., active hallucinations, thought disorder) that would impair the individual's ability to provide true informed consent or participate in the baseline survey
- Visibly distraught (e.g., suicidal, homicidal, exhibiting violent behavior) at the time of consent or the baseline survey or
- Intoxicated or under the influence of alcohol or other substances to such an extent that in the opinion of the study staff, the ability to give true informed consent or to understand and answer the questions is impaired.

With the reduction in the award funding the scope of work of the study was reduced to not include additional enrollment activities as communicated with the NIH prior to the funding award. In 2022, it was determined by the MPIs that some additional enrollment activities could be supported with current funds. Approval was obtained from the program officer to revise the study aims to allow for enrolling participants with a focus on recruiting mostly ethnic/racial minority youth and young adults. Therefore, the inclusion criteria for the GnRHa cohort and the GAH transmasculine cohort that the participants identify as a youth of color with an emphasis on non-Hispanic/Latinx youth was revised to be a focus in recruitment but not a strict eligibility criterion.

The inclusion criteria for the late pubertal cohort participants in the GAH cohort were revised from a minimum age of 8 years to 12 years as approved by the program officer on 4/19/22. The rationale for this change is because this is an observational study, in the original proposal, the MPIs wanted to ensure that the study could enroll potential participants younger than 12, if they were initiating gender-affirming hormones. From reviewing study data, the MPIs found that the youngest age in the late pubertal, GAH cohort was 12 years. Therefore, the eligibility criteria were revised to match the study population.

The research is being conducted at Children's Hospital Los Angeles (CHLA), Ann & Robert H. Lurie Children's Hospital of Chicago, Boston Children's Hospital, and University of California San Francisco Benioff Children's Hospitals San Francisco and Oakland. These four academic hospitals are situated strategically across the country and have dedicated transgender youth clinics. They are considered the national leaders in the care of transgender children, adolescents, and young adults. 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.

The four collaborating sites will recruit and enroll child and parent/caregiver participants, conduct study activities, and provide data to the data core at CHLA. The principal investigators will oversee all aspects of the study process and will monitor implementation of study activities. They will maintain ongoing communication through conference calls in order to be responsive to any issues that may arise and will modify the protocol if needed.

b. Study Procedures, Materials, and Potential Risks

Data will be collected directly from participants and their parents or caregiver via a computerized survey or by interview to minimize concerns about confidentiality, encourage honest responses to sensitive issues, and allow completion of the survey at the participants' own pace. Demographic data collected will include items such as age, ethnicity, educational level and birth city/country, as well as data specific to the transgender population, such as age parents realized their child's transgender identity, age of youth participant first living in the desired gender role, and contexts in which the child is living in their desired gender role, if any. The computerized survey will also collect information from the parents and youth regarding data such as physical activity and dietary calcium intake and psychosocial assessments such as

the degree of social gender transition, parental support for gender diversity, parenting stress, quality of life, resiliency, anxiety, self-harm, social connectedness, etc. Interviews will be used for obtaining mental health diagnosis information through the use of the MINI and MINI Kid and for obtaining information regarding diagnoses and medications that may not be detailed in the electronic health record. In addition, case report forms (CRFs) will be used for items such as tracking the Modified Ferriman-Gallwey score, Tanner staging, medication information, diagnoses, etc.

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. The CHLA coordinating center staff may have access to individually identifiable private information about the participants when providing on-site technical assistance for study implementation and quality assurance activities.

No personal identifying information (e.g., name, tracking information, etc.) will be placed on any of the CRFs or collected within the computerized 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.

For the computerized baseline and follow-up surveys each participant will be assigned a code and their 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. The coordinating center staff will not have access to the sites' key to the codes.

Computerized data will be collected via QDS software and web-based services (e.g., REDCap, ASEBA) at the collaborating sites. 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 to CHLA. A password will be used to access survey data and will be made accessible only to the MPIs 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. Study-wide data management procedures, including integration and verification of multi-site data, will take place at CHLA.

The potential 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 surveys. 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. Informed Consent and Assent
Study team members will recruit participants for the study by speaking with patients and their parents/legally authorized representatives face-to-face or by telephone. Information regarding the study will be provided and interest in participation will be assessed.

If potential participants are interested in enrolling in the study, staff members from Children's Hospital Los Angeles, Lurie Children's Hospital of Chicago, Boston Children's Hospital, and University of California at San Francisco who have received IRB certification will consent participants. All research participants will

review and sign an informed consent/permission/assent form. 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 site Principal Investigator and the IRB. A waiver of some or all of the elements of informed consent will not be sought.

For child participants aged 8 to 17 years old, the participant will sign an assent form and the parent/legally authorized representative will sign a parental permission form. Young adult participants 18 and older will sign a consent form. If a youth participant turns 18 while on the study, they will sign a consent addendum. All parent/caregiver participants will provide written consent for their own participation in the study. Informed consent, assent, permission will be obtained before any research activities are conducted.

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.

Project staff will inform participants that they have the right to skip any questions during the computerized survey or face-to-face interview 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).

b. Protection 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 or medical record numbers) of the participants will appear in any computer or paper 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.

Data will remain on the CHLA server or secure, HIPAA compliant web applications (REDCap and ASEBA) during data collection, verification, cleaning, and analysis. CHLA will continue to serve as the repository for intact versions of the study's comprehensive data sets. The most up-to-date data set (as well as site-specific data), including scored measures and created scales, will be made readily available to all PIs. To meet NIH obligations for data sharing, other investigators not affiliated with the study will also have access de-identified study data pursuant to a signed Data Use Agreement. The Contact PI (Dr. Olson-Kennedy of CHLA) will be responsible for maintaining Data Use Agreement records and secure transmission of data to outside investigators.

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. All of the sites have licensed psychologists who provide clinical care to

transgender and gender nonconforming children. Participants do not have to answer any question in the computerized or face-to-face 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.

A possible adverse event that is anticipated includes the need to violate participant confidentiality due to risk of harm to self or child abuse. Study personnel will be trained regarding the limits of confidentiality. This training will include reviewing possible scenarios and knowledge of key questions to assess risk. We will train staff to err on the side of caution and to contact a supervisor as needed. Supervisors will be available by phone 24 hours a day should staff need to consult regarding an emergency. In this situation, we will train staff members to leave participants in the company of study personnel and immediately contact supervisors before participants leave. Under the guidance of supervisors, staff will be trained either to ensure the safety of participants (i.e., call the police, or if appropriate, to escort participants to the emergency room).

Unanticipated adverse events will be brought to the attention of the MPIs and reported immediately to all relevant IRBs. The IRBs will determine whether it is appropriate to stop the study protocol temporarily or will provide suggestions/modifications to the study procedures. Any recommendations from local IRBs will be communicated to the IRB of Record at CHLA. Possible modifications include adding these possible adverse events to the consent form and re-consenting all study participants. The PI will be responsible for monitoring participant safety on a monthly basis at regularly scheduled research meetings. They will keep a written log of all adverse events and ensure that the IRB is contacted immediately. They will also keep a log of the outcome of IRB decisions regarding adverse events and apprise the research team of any changes that need to be made as a result of IRB decisions.

c. Vulnerable Subjects
This proposal involves children, a vulnerable subject population. The protocol will be certified through the IRB of Record, which is located at a children's hospital, and the research staff 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 legally authorized representatives and for assent by children will be followed. All HHS Subpart D – Additional Protections for Children will be followed. Within the first two months of funding, the project staff will submit an application to the single IRB for protocol approval. Throughout the project, staff will continue to work with the IRB to protect the rights and confidentiality of all individuals who participate in data collection.

Potential Benefits of the Proposed Research to Research Participants and Others
While there are no potential direct benefits to the research participants, possible risks (i.e. discomfort answering questions, potential confidentiality breeches) are minimal and are outweighed by the anticipated societal benefits.

Importance of the Knowledge to be Gained
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.

SINGLE IRB PLAN

During the current grant cycle, the study has been reviewed and approved by all of the four institutional IRBs. For the renewal grant period, the study will transition to a single Institutional Review Board (sIRB), and Children's Hospital Los Angeles (CHLA) will fulfill the role of IRB of Record for this study. CHLA has extensive experience as a single IRB (sIRB) and as an IRB of record for pediatric research consortia. It obtained accreditation from the Association for the Accreditation of Human Research Protection Programs, Inc., in 2012, recognizing its commitment to the protection of human research participants through the highest ethical standards. CHLA sIRB activities are supported through the CHLA Human Subjects Protection Program, which follows all regulatory requirements including those from the Department of Health and Human Services (DHHS) at 45 CFR 46, the Food and Drug Administration (FDA) at 21 CFR 50 and 56, the Health Insurance Portability and Accountability Act (HIPAA) at 45 CFR 160 and 64 and any and all other regulatory requirements affecting research with humans including local and state laws and ordinances. The CHLA IRB is well qualified to meet the Final NIH Policy on the Use of a Single Institution Review Board for Multi-Site Research.

All sites have agreed that the Children's Hospital Los Angeles IRB will serve as the sIRB of record and to rely on the proposed sIRB. If an additional site was to be added after award, it will rely on the sIRB.

Communication between sites and the sIRB will be conducted at two levels. The Director of the Human Subjects Protection Program at CHLA and the sites will communicate to establish a reliance agreement. All sites are members of the SMART IRB Reliance platform, which will facilitate communication during the reliance process. The CHLA Clinical Research Manager will communicate with each site's study coordinator/research associate regarding information that needs to be relayed to the local IRB or vice versa. Communication will support the local context for research, ensuring that the research teams follow local laws and regulations where they will be conducting research. In addition, information may be needed regarding local customs and literacy. Documentation will be provided to the relying sites of all amendments to the protocol to ensure that all sites are implementing the protocol with fidelity and that relying IRBs have accurate information regarding research activities being conducted at their institution. Locally-relevant reportable events (such a serious adverse events or protocol deviations) will be submitted to both the local IRB and the CHLA sIRB. CHLA and the sites are experienced in this relationship as CHLA is the coordinating center for the current multi-site R01HD097122, A Longitudinal Study of Gender Nonconformity in Prepubescent Children.

All participating sites will, prior to initiating the study, sign an authorization/reliance agreement that will clarify the roles and responsibilities of the sIRB and participating sites.

CHLA will maintain records of the authorization/reliance agreements and of the communication plan.

DATA AND SAFETY MONITORING PLAN

This study is a minimal risk, observational study and does not meet the NIH definition of a clinical trial. Nevertheless, there still remains a risk of an adverse event. The most likely occurrence would be related to answering or responding to questions about sensitive topics that may be uncomfortable or upsetting. In the event of said situation, the study coordinators are trained to contact a licensed clinician to respond to the situation immediately. Any adverse events or unanticipated problems are reported to the coordinating center clinical research manager in order for them to be reported to the IRB of record. In addition, as a DSMB is not required of this study, any unanticipated problem or adverse events are discussed on the monthly MPI call to ensure awareness and oversight.

Data monitoring is conducted by the data manager and the data analyst at the Coordinating Center. Data that are submitted by the sites are reviewed for completeness and accuracy and to ensure incoming data are of high quality. The data analyst will run ongoing analyses as the cohorts move through the data points. If any data items are unclear or of concern, the data analyst sends a query to the study coordinator and tracks the query until the response is complete. The data manager provides updates regarding the data and analyses being conducted to the MPIs during the monthly MPI calls, and if a concern was found during an analysis of the observational, clinical data, it would be reported to the MPIs for safety discussions.

OVERALL STRUCTURE OF THE STUDY TEAM

The overall structure of the study team is as follows. Also, please reference the Multiple Principal Investigator Leadership Plan.

Four Study Sites

- Principal Investigator – responsible for all study activities occurring at the site and for coordinating with the other MPIs for overall study communication regarding: human subjects protection, NIH reporting, study implementation, data analysis, and publication. Please see the MPI Leadership Plan for more detail.
- Co-Investigator – collaborate with the Co-Is at the other sites to obtain meaningful mental health information form the youth, young adult, and parent/caregiver participants; conduct data analysis; and disseminate results.
- Study Coordinator – recruit and enroll study participants, conduct informed consent conferences, conduct study activities, accurately obtain and record data, participate in monthly study coordinator calls, report concerns to the site PI.
- Biostatician – collaborate with the PIs and Co-Is to conduct analyses of the medical and mental health data for publication.

Coordinating Center & Subaward Site

- Contact Principal Investigator – responsible for coordination of the MPIs and overseeing the coordinating center.
- Co-Investigators – responsible for making final decisions regarding instruments and data collection tools; oversee and direct quantitative data management and analysis and provide advanced statistical consultation to the project, including developing and executing analytical plans and advising the data team on appropriate longitudinal data analysis methods and procedures. Work closely with the biostaticians to ensure clear communication and coordination between sites on analytical and data-related issues. Provide guidance regarding strategies to diversify the study population.
- Data Analyst – conduct activities such as data cleaning, ensuring that data are complete, querying the study coordinators about problematic data, running analyses, providing data to the protocol team, and assisting with interpretation of analysis results.
- Research Manager – oversees the data management system, data cleaning and merging, and data analysis activities; coordinates the Data Coordination Committee.
- Clinical Research Manager – responsible for all activities related to the sIRB; amends the protocol as needed; communicates with all of the study coordinators regarding the study protocol through facilitating monthly calls; provides technical assistance; conducts quality assurance activities.
- Database Manager – maintains and updates the database that collects participant clinical data and creates reports to support study implementation and data analysis.

Section 4 - Protocol Synopsis (Study 324174)

4.1. Study Design

4.1.a. Detailed Description

4.1.b. Primary Purpose

4.1.c. Interventions

Type	Name	Description

4.1.d. Study Phase

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

4.1.e. Intervention Model

4.1.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.1.g. Allocation

4.2. Outcome Measures

Type	Name	Time Frame	Brief Description

4.3. Statistical Design and Power

4.4. Subject Participation Duration

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

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

4.6. Is this an applicable clinical trial under FDAAA? (SEE SECTION 6.6)

4.7. Dissemination Plan

Section 6 - Clinical Trial Milestone Plan (Study 324174)

6.1. Study Primary Completion Date		
6.2. Study Final Completion Date		
6.3. Enrollment and randomization		
Enrollment of the First Participant (Study Start Date)	07/25/2016	Actual
25% of planned enrollment recruited by		
50% of planned enrollment recruited by		
75% of planned enrollment recruited by		
100% of planned enrollment recruited by		
6.4. Completion of primary endpoint data analyses		
6.5. Reporting of results in ClinicalTrials.gov		
6.6. Is this an applicable clinical trial under FDAAA?	○ Yes	● No

I. OUTCOMES

I.1 What were the outcomes of the award?

The Trans Youth Care – United States (TYCUS) study investigated outcomes for transgender and nonbinary (TNB) youth starting medical treatments for gender affirmation. The study design was observational, and these treatments were provided as part of the participants' clinical care (not by the research study) and consisted of medications to pause the progress of puberty ("blockers") and/or estrogen or testosterone (gender-affirming hormones, or "GAH"). The study collected data on psychosocial and physical outcomes at baseline (prior to starting any medical treatments) then every 6 to 12 months after participants started treatments.

Our main findings for youth starting treatment with blockers include:
• At baseline, about one-quarter of these youth had clinically concerning scores for depression and anxiety. About one-quarter reported having thought about suicide, and 8% reported having attempted suicide in the past. These numbers are on par with the population of middle school youth at large.
• Over 2 years of medical intervention that started with blockers, mental health remained relatively stable and was on par with the population at large. These youth showed no worsening of their mental or emotional health and suicidality decreased from baseline to 24 months. Mean scores on mental health measures remain stable in a clinically non-significant range over two years.
• At baseline, these youth already have lower amounts of calcium in their bones (bone-mineral density) than the general population; this may be related to lower levels of physical activity.

Our main findings for youth starting treatment with GAH include:
• At baseline, about half of these youth had clinically concerning scores for depression and anxiety. About two-thirds reported having thought about suicide, and one-quarter reported having attempted.
• By two years after starting GAH, these youth showed increased scores for life satisfaction, appearance congruence (having the physical appearance of one's body match one's gender identity), positive emotions, and psychological well-being and decreased scores for depression and anxiety.
• At baseline, these youth have lower levels of high-density lipoprotein cholesterol (HDL cholesterol, the "good" cholesterol) than the general population but otherwise have similar weights, blood pressures, and levels of low-density lipoprotein cholesterol (LDL cholesterol, the "bad" cholesterol)
• By two years after starting GAH, youth starting estrogen showed increases in HDL cholesterol and decreases in LDL cholesterol, while youth starting testosterone showed decreases in HDL cholesterol and increases in LDL cholesterol. These changes are consistent with known effects of these hormones.

FEDERAL FINANCIAL REPORT

FINAL

1. Federal Agency and Organizational Element to Which Report is Submitted National Institutes of Health		**2. Federal Grant or Other Identifying Number Assigned by Federal Agency** RHD082554B		
3.Recipient Organization (Name and complete address, including Zip code) CHILDREN'S HOSPITAL LOS ANGELES 4650 Sunset Boulevard Mailstop #97 LOS ANGELES CA 900276062				
4a. UEI Number DVL1CMRMWRN9	**4b. EIN** 1956121916A1	**5. Recipient Account Number or Identifying Number** 2220P	**6. Report Type** ☐ Quarterly ☐ Semi-Annual ☐ Annual ☒ Final	**7. Basis of Accounting** ☐ Cash ☒ Accrual
8. Project/Grant Period **From:** 08/01/2015		**To:** 07/31/2025	**9. Reporting Period End Date** 07/31/2025	

10. Transactions	**Cumulative**
(Use lines a-c for single or multiple grant reporting)	
Federal Cash (To report multiple grants, also use FFR Attachment):	
a. Cash Receipts	$3,979,164.03
b. Cash Disbursements	$3,979,164.03
c. Cash on Hand (line a minus b)	$0.00
(Use lines d-o for single grant reporting)	
Federal Expenditures and Unobligated Balance:	
d. Total Federal funds authorized	$3,979,164.03
e. Federal share of expenditures	$3,979,164.03
f. Federal share of unliquidated obligations	$0.00
g. Total Federal share (sum of lines e and f)	$3,979,164.03
h. Unobligated balance of Federal funds (line d minus g)	$0.00
Recipient Share:	
i. Total recipient share required	$0.00
j. Recipient share of expenditures	$0.00
k. Remaining recipient share to be provided (line i minus j)	$0.00
Program Income:	
l. Total Federal program income earned	$0.00
m. Program income expended in accordance with the deduction alternative	$0.00
n. Program income expended in accordance with the addition alternative	$0.00
o. Unexpended program income (line l minus line m or line n)	$0.00

11. Indirect Expense	**a. Type**	**b. Rate**	**c. Period From**	**Period To**	**d. Base**	**e. Amount Charged**	**f. Federal Share**
	Final	69.5	08/01/2015	07/31/2025	$1,329,103.42	$923,726.88	$923,726.86
				g. Totals:	$1,329,103.42	$923,726.88	$923,726.86

12. Remarks: Attach any explanations deemed necessary or information required by Federal sponsoring agency in compliance with governing legislation:

NIH Comment: Accepted By: Cindy Ampabeng Date Report Accepted: 12/5/2025.

13. Certification: By signing this report, I certify to the best of my knowledge and belief that the report is true, complete, and accurate, and the expenditures, disbursements and cash receipts are for the purposes and intent set forth in the award documents. I am aware that any false, fictitious, or fraudulent information may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

a. Typed or Printed Name and Title of Authorized Certifying Official Ozuna, Alexis Post-Award Analyst	**c. Telephone (Area code, number and extension)** **d. Email address** alozuna@chla.usc.edu
b. Signature of Authorized Certifying Official	**e. Date Report Submitted (Month, Day, Year)** 11/28/2025
	14. Agency use only: Accepted by: Ampabeng, Cindy Date Report Accepted: 12/05/2025

Standard Form 425
OMB Approval Number: 0404-0014
Expiration Date: 02/28/2022