Recipient Information

1. Recipient Name
CHILDRENS HOSPITAL MEDICAL CENTER
3333 BURNET AVE
CINCINNATI, OH 45229

2. Congressional District of Recipient
01

3. Payment System Identifier (ID)
1310833936A1

4. Employer Identification Number (EIN)
310833936

5. Data Universal Numbering System (DUNS)
071284913

6. Recipient's Unique Entity Identifier
JZD1HLM2ZU83

7. Project Director or Principal Investigator
Tanya L. Kowalczyk Mullins, MD

(b)(6)

8. Authorized Official
(b)(6)

Federal Agency Information

9. Awarding Agency Contact Information
TANYA PATRICE Smith

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
TANYA.SMITH@NIH.GOV

10. Program Official Contact Information
BENYAM Hailu
Medical Officer
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
benyam.hailu@nih.gov
301-402-1366

Federal Award Information

11. Award Number
5R01HL161153-02

12. Unique Federal Award Identification Number (FAIN)
R01HL161153

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy

15. Assistance Listing Number
93.839

16. Assistance Listing Program Title
Blood Diseases and Resources Research

17. Award Action Type
Non-Competing Continuation

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 08/01/2023 – **End Date** 07/31/2024	
20. Total Amount of Federal Funds Obligated by this Action	$626,730
20 a. Direct Cost Amount	$394,170
20 b. Indirect Cost Amount	$232,560
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$626,730
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$626,730
26. Project Period Start Date 08/01/2022 – **End Date** 07/31/2027	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$1,077,284

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Andre D Walker

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

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RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

SECTION I – AWARD DATA – 5R01HL161153-02

Principal Investigator(s):
Tanya L. Kowalczyk Mullins, MD

Award e-mailed to: sponsoredresearch@cchmc.org

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $626,730 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to CINCINNATI CHILDRENS HOSP MED CTR in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01HL161153. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Andre D Walker
Grants Management Officer
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Additional information follows

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Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$242,809
Fringe Benefits	$67,501
Personnel Costs (Subtotal)	$310,310
Travel	$6,210
Other	$76,150
Publication Costs	$1,500
Federal Direct Costs	$394,170
Federal F&A Costs	$232,560
Approved Budget	$626,730
Total Amount of Federal Funds Authorized (Federal Share)	$626,730
TOTAL FEDERAL AWARD AMOUNT	$626,730
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$626,730

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$626,730	$626,730
3	$630,774	$630,774
4	$600,769	$600,769
5	$555,335	$555,335

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1310833936A1
Document Number:	RHL161153A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2023

IC	CAN	2023	2024	2025	2026
HL	8475152	$626,730	$630,774	$600,769	$555,335

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: BB N / **OC**: 41025 / **Released**: Walker, Andre 06/23/2023
Award Processed: 06/27/2023 12:11:46 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5R01HL161153-02

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 5R01HL161153-02

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01HL161153. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights laws enforced by HHS. See https://www.hhs.gov/civil-rights/for-providers/provider-

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obligations/index.html and https://www.hhs.gov/.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html and https://www.lep.gov.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html.
- HHS funded health and education programs must be administered in an environment free of sexual harassment; see https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html. For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see https://grants.nih.gov/grants/policy/harassment.htm.
- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see https://www.hhs.gov/conscience/conscience-protections/index.html and https://www.hhs.gov/conscience/religious-freedom/index.html.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – HL SPECIFIC AWARD CONDITIONS – 5R01HL161153-02

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

NHLBI FUNDING GUIDELINES

This award is being issued in accordance with the NHLBI FY 2023 Operating Guidelines which can be found at: https://www.nhlbi.nih.gov/current-operating-guidelines

PRIOR APPROVAL REQUEST

It is recommended that applicable prior approval requests be submitted via the eRA Commons Prior Approval Module (link: prior_approval (nih.gov)). Please refer to Part II Chapter 8 of the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

NON-COMPETING RENEWAL (SNAP)

The NIH requires the use of the Research Performance Progress Report (RPPR) for all Type 5 progress reports. The RPPR and other documents applicable to this SNAP grant

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are due the 15th of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/15). Please see http://grants.nih.gov/grants/rppr/index.htm for additional information on the RPPR.

SPREADSHEET SUMMARY
AWARD NUMBER: 5R01HL161153-02

INSTITUTION: CINCINNATI CHILDRENS HOSP MED CTR

Budget	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$242,809	$242,809	$232,844	$232,844
Fringe Benefits	$67,501	$67,501	$64,731	$64,731
Personnel Costs (Subtotal)	$310,310	$310,310	$297,575	$297,575
Travel	$6,210	$7,526	$4,960	$3,340
Other	$76,150	$78,877	$75,307	$46,852
Publication Costs	$1,500			$1,500
TOTAL FEDERAL DC	$394,170	$396,713	$377,842	$349,267
TOTAL FEDERAL F&A	$232,560	$234,061	$222,927	$206,068
TOTAL COST	$626,730	$630,774	$600,769	$555,335

Facilities and Administrative Costs	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	59%	59%	59%	59%
F&A Cost Base 1	$394,170	$396,713	$377,842	$349,267
F&A Costs 1	$232,560	$234,061	$222,927	$206,068

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Department of Health and Human Services
National Institutes of Health
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Notice of Award
FAIN# R01HL161153
Federal Award Date
08-18-2022

Recipient Information

1. Recipient Name
CHILDREN'S HOSPITAL MEDICAL CENTER
3333 BURNET AVE

CINCINNATI, 45229

2. Congressional District of Recipient
01

3. Payment System Identifier (ID)
1310833936A1

4. Employer Identification Number (EIN)
310833936

5. Data Universal Numbering System (DUNS)
071284913

6. Recipient's Unique Entity Identifier
JZD1HLM2ZU83

7. Project Director or Principal Investigator
Tanya L. Kowalczyk Mullins, MD

(b)(6)

8. Authorized Official
(b)(6)

Federal Agency Information

9. Awarding Agency Contact Information
TANYA PATRICE Smith

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
TANYA.SMITH@NIH.GOV

10. Program Official Contact Information
BENYAM Hailu
Medical Officer
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
benyam.hailu@nih.gov
301-402-1366

Federal Award Information

11. Award Number
1R01HL161153-01A1

12. Unique Federal Award Identification Number (FAIN)
R01HL161153

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy

15. Assistance Listing Number
93.839

16. Assistance Listing Program Title
Blood Diseases and Resources Research

17. Award Action Type
New Competing (REVISED)

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 08-01-2022 **– End Date** 07-31-2023	
20. Total Amount of Federal Funds Obligated by this Action	$0
20 a. Direct Cost Amount	$0
20 b. Indirect Cost Amount	$0
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$450,554
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$450,554
26. Project Period Start Date 08-01-2022 **– End Date** 07-31-2027	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$450,554

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Andre D Walker

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise

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requested from the grant payment system.

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

SECTION I – AWARD DATA – 1R01HL161153-01A1 REVISED

Principal Investigator(s):
Tanya L. Kowalczyk Mullins, MD

Award e-mailed to: sponsoredresearch@cchmc.org

Dear Authorized Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to CINCINNATI CHILDRENS HOSP MED CTR in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01HL161153. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Andre D Walker
Grants Management Officer
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Additional information follows

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Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$197,079
Fringe Benefits	$54,788
Personnel Costs (Subtotal)	$251,867
Travel	$4,590
Other	$26,910
Federal Direct Costs	$283,367
Federal F&A Costs	$167,187
Approved Budget	$450,554
Total Amount of Federal Funds Authorized (Federal Share)	$450,554
TOTAL FEDERAL AWARD AMOUNT	$450,554
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$450,554	$450,554
2	$626,730	$626,730
3	$630,774	$630,774
4	$600,769	$600,769
5	$555,335	$555,335

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1310833936A1
Document Number:	RHL161153A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2022

IC	CAN	2022	2023	2024	2025	2026
HL	8475152	$450,554	$626,730	$630,774	$600,769	$555,335

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: BB N / **OC**: 41021 / **Released**: Walker, Andre 08-17-2022
Award Processed: 08/18/2022 12:09:12 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R01HL161153-01A1 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 1R01HL161153-01A1 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

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a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01HL161153. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System

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(FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – HL SPECIFIC AWARD CONDITIONS – 1R01HL161153-01A1 REVISED

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

REVISION #1 – Year 5

This award is revised to address the following issue:

The inclusion of year 5 to the award budget as this project is a Clinical Study. All previous terms and conditions remain in effect.

NHLBI FUNDING GUIDELINES

This award is being issued in accordance with the NHLBI FY 2022 Operating Guidelines which can be found at: https://www.nhlbi.nih.gov/current-operating-guidelines

SALARY CAP

None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap.

Current salary cap levels can be found at the following URL: http://grants.nih.gov/grants/policy/salcap_summary.htm.

PRIOR APPROVAL REQUEST

It is recommended that applicable prior approval requests be submitted via the eRA Commons Prior Approval Module (link: prior_approval (nih.gov)). Please refer to Part II Chapter 8 of the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

NON-COMPETING RENEWAL (SNAP)

The NIH requires the use of the Research Performance Progress Report (RPPR) for all Type 5 progress reports. The RPPR and other documents applicable to this SNAP grant are due the 15th of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/15). Please see http://grants.nih.gov/grants/rppr/index.htm for additional information on the RPPR.

SPREADSHEET SUMMARY

AWARD NUMBER: 1R01HL161153-01A1 REVISED

INSTITUTION: CINCINNATI CHILDRENS HOSP MED CTR

Budget	Year 1	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$197,079	$242,809	$242,809	$232,844	$232,844
Fringe Benefits	$54,788	$67,501	$67,501	$64,731	$64,731
Personnel Costs (Subtotal)	$251,867	$310,310	$310,310	$297,575	$297,575

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Travel	$4,590	$6,210	$7,526	$4,960	$3,340
Other	$26,910	$76,150	$78,877	$75,307	$46,852
Publication Costs		$1,500			$1,500
TOTAL FEDERAL DC	$283,367	$394,170	$396,713	$377,842	$349,267
TOTAL FEDERAL F&A	$167,187	$232,560	$234,061	$222,927	$206,068
TOTAL COST	$450,554	$626,730	$630,774	$600,769	$555,335

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	59%	59%	59%	59%	59%
F&A Cost Base 1	$283,367	$394,170	$396,713	$377,842	$349,267
F&A Costs 1	$167,187	$232,560	$234,061	$222,927	$206,068

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Department of Health and Human Services
National Institutes of Health
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Notice of Award
FAIN# R01HL161153
Federal Award Date
07-31-2022

Recipient Information

1. Recipient Name
CHILDREN'S HOSPITAL MEDICAL CENTER
3333 BURNET AVE

CINCINNATI, 45229

2. Congressional District of Recipient
01

3. Payment System Identifier (ID)
1310833936A1

4. Employer Identification Number (EIN)
310833936

5. Data Universal Numbering System (DUNS)
071284913

6. Recipient's Unique Entity Identifier
JZD1HLM2ZU83

7. Project Director or Principal Investigator
Tanya L. Kowalczyk Mullins, MD

(b)(6)

8. Authorized Official
(b)(6)

Federal Agency Information

9. Awarding Agency Contact Information
TANYA PATRICE Smith

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
TANYA.SMITH@NIH.GOV

10. Program Official Contact Information
BENYAM Hailu
Medical Officer
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
benyam.hailu@nih.gov
301-402-1366

Federal Award Information

11. Award Number
1R01HL161153-01A1

12. Unique Federal Award Identification Number (FAIN)
R01HL161153

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy

15. Assistance Listing Number
93.839

16. Assistance Listing Program Title
Blood Diseases and Resources Research

17. Award Action Type
New Competing

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 08-01-2022 **– End Date** 07-31-2023	
20. Total Amount of Federal Funds Obligated by this Action	$450,554
20 a. Direct Cost Amount	$283,367
20 b. Indirect Cost Amount	$167,187
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$450,554
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$450,554
26. Project Period Start Date 08-01-2022 **– End Date** 07-31-2026	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$450,554

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Andre D Walker

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise

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requested from the grant payment system.

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

SECTION I – AWARD DATA – 1R01HL161153-01A1

Principal Investigator(s):
Tanya L. Kowalczyk Mullins, MD

Award e-mailed to: sponsoredresearch@cchmc.org

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $450,554 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to CINCINNATI CHILDRENS HOSP MED CTR in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01HL161153. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Andre D Walker
Grants Management Officer
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Additional information follows

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Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$197,079
Fringe Benefits	$54,788
Personnel Costs (Subtotal)	$251,867
Travel	$4,590
Other	$26,910
Federal Direct Costs	$283,367
Federal F&A Costs	$167,187
Approved Budget	$450,554
Total Amount of Federal Funds Authorized (Federal Share)	$450,554
TOTAL FEDERAL AWARD AMOUNT	$450,554
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$450,554

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$450,554	$450,554
2	$624,155	$624,155
3	$626,105	$626,105
4	$600,180	$600,180

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1310833936A1
Document Number:	RHL161153A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2022

IC	CAN	2022	2023	2024	2025
HL	8475152	$450,554	$624,155	$626,105	$600,180

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: BB N / **OC**: 41021 / **Released**: Walker, Andre 07-25-2022
Award Processed: 07/31/2022 08:09:20 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R01HL161153-01A1

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 1R01HL161153-01A1

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

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a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01HL161153. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System

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(FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – HL SPECIFIC AWARD CONDITIONS – 1R01HL161153-01A1

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

SPREADSHEET SUMMARY

AWARD NUMBER: 1R01HL161153-01A1

INSTITUTION: CINCINNATI CHILDRENS HOSP MED CTR

Budget	Year 1	Year 2	Year 3	Year 4
Salaries and Wages	$197,079	$242,809	$242,809	$232,844
Fringe Benefits	$54,788	$67,501	$67,501	$64,731
Personnel Costs (Subtotal)	$251,867	$310,310	$310,310	$297,575
Travel	$4,590	$4,590	$4,590	$4,590
Other	$26,910	$76,150	$78,877	$75,307
Publication Costs		$1,500		
TOTAL FEDERAL DC	$283,367	$392,550	$393,777	$377,472
TOTAL FEDERAL F&A	$167,187	$231,605	$232,328	$222,708
TOTAL COST	$450,554	$624,155	$626,105	$600,180

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4
F&A Cost Rate 1	59%	59%	59%	59%
F&A Cost Base 1	$283,367	$392,550	$393,777	$377,472
F&A Costs 1	$167,187	$231,605	$232,328	$222,708

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PI: **Mullins, Tanya L. Kowalczyk**	Title: Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy	
Received: 11/05/2021	Opportunity: PA-20-185	Council: 05/2022
Competition ID: FORMS-F	FOA Title: NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed)	
1R01HL161153-01A1	Dual: HD	Accession Number: 4647702
IPF: 615001	Organization: CINCINNATI CHILDRENS HOSP MED CTR	
Former Number: 1R01HL161153-01	Department: Pediatrics	
IRG/SRG: HHD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 283,367 Year 2: 398,518 Year 3: 405,471 Year 4: 390,975 Year 5: 366,908	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N HFT: N	New Investigator: Y Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Tanya Mullins	Children's Hospital Medical Center	PD/PI
(b)(6)	Children's Hospital Medical Center	Co-Investigator
	Children's Hospital Medical Center	Other (Specify)-Collaborator
	Children's Hospital Medical Center	Other (Specify)-Collaborator
	Children's Hospital Medical Center	Other (Specify)-Collaborator
	Children's Hospital Medical Center	Other (Specify)-Biostatistician

Appendices

Appendix_1_Aim_2_Phase_1_Draft_Interview(b)(6)

OMB Number: 4040-0010
Expiration Date: 12/31/2022

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
HL161153

b. Agency Routing Number

2. DATE SUBMITTED

Application Identifier
FP00008475_Res1

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: 071284913

Legal Name*: Children's Hospital Medical Center
Department: Pediatrics
Division: Adolescent and Transition Med
Street1*: 3333 Burnet Avenue
Street2: (b)(6)
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 452293039

Person to be contacted on matters involving this application
Prefix: First Name*: (b)(6) Middle Name: Last Name*: (b)(6) Suffix:
Position/Title: SPEC III-SPONS RSCH
Street1*: 3333 Burnet Avenue
Street2:
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 452293039
Phone Number*: (b)(6) Fax Number: Email: sponsoredresearch@cchmc.org

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 31-0833936

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

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

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

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

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

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE: NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed)

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy

12. PROPOSED PROJECT

Start Date* 07/01/2022
Ending Date* 06/30/2027

13. CONGRESSIONAL DISTRICTS OF APPLICANT
OH-001

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Tanya Middle Name: Lilliane Kowalczyk Last Name*: Mullins Suffix:
Position/Title: ASSOCIATE PROFESSOR
Organization Name*: Children's Hospital Medical Center
Department: Pediatrics
Division: Adolescent and Transition Med
Street1*: 3333 Burnet Avenue
Street2: (b)(6)
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 452290000
Phone Number*: (b)(6) Fax Number: (b)(6) Email*: (b)(6)

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$2,933,931.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$2,933,931.00
d. Estimated Program Income*	$0.00

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

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

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

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

● I agree*

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

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: (b)(6) Middle Name: Last Name*: (b)(6) Suffix:
Position/Title*: SR DIRECTOR-SRS
Organization Name*: Children's Hospital Medical Center
Department: Sponsored Programs
Division: Sponsored Programs
Street1*: 3333 Burnet Avenue
Street2:
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 452293039
Phone Number*: (b)(6) Fax Number: Email*: sponsoredresearch@cchmc.org

Signature of Authorized Representative*
(b)(6)

Date Signed*
11/04/2021

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 12/31/2022

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Children's Hospital Medical Center
Duns Number:	071284913
Street1*:	3333 Burnet Avenue
Street2:	
City*:	Cincinnati
County:	Hamilton
State*:	OH: Ohio
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	452293039
Project/Performance Site Congressional District*:	OH-001

Additional Location(s) File Name:

Funding Opportunity Number: PA-20-185. Received Date: 2021-11-05T08:26:18.000-04:00

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED Other Project Information

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

1.a. If YES to Human Subjects

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

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

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

IRB Approval Date:

Human Subject Assurance Number 00002988

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

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

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

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

4.b. If yes, please explain:

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

4.d. If yes, please explain:

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

5.a. If yes, please explain:

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

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary_.pdf
8. Project Narrative*	Project_Narrative_.pdf
9. Bibliography & References Cited	References_Cited.pdf
10.Facilities & Other Resources	Facilities_and_Other_Resources.pdf
11.Equipment	Equipment.pdf

Funding Opportunity Number: PA-20-185. Received Date: 2021-11-05T08:26:18.000-04:00

PROJECT SUMMARY

Gender-affirming hormone therapy (GAHT) is one of the most effective interventions for treating gender dysphoria in transgender and gender nonconforming (hereafter transgender) youth, thereby reducing suicide risk. GAHT, particularly estrogen, may increase the risk of thrombosis. While hematologists often evaluate patients before GAHT start who are at risk of thrombosis due to personal/family risk factors, there are no guidelines or data to inform management. This lack of data leads to significant variation in clinical practice that may compromise care. Because this knowledge gap hinders the ability of gender care clinicians and hematologists to provide optimal care to transgender youth, the objectives of this proposal are to prospectively examine biologic changes associated with thrombotic risk in a cohort of transgender youth receiving estrogen GAHT and to examine the attitudes and practices of clinicians who make decisions about thromboprophylaxis for youth on GAHT. The proposed work is relevant to the priorities of understanding human biology (defining changes in thrombotic risk associated with estrogen GAHT) and reducing human disease (defining which transgender youth may benefit from thromboprophylaxis). The proposed research is innovative in the focus on transgender youth, comprehensive examination of changes in coagulation factors in youth using estrogen GAHT, and determination of factors influencing the treatment recommendations of hematologists for thromboprophylaxis among transgender youth with personal/family risk factors for thrombosis. The specific aims are to: 1) prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen GAHT in a population of transgender women (up to age 22 years at GAHT start); and 2) characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to TG youth with personal/family risk factors for thrombosis. In Aim 1, 75 transgender women up to 22 years of age who are starting estrogen GAHT will undergo thorough and systematic evaluation of hemostatic factors at baseline prior to GAHT start, and then at 3, 6, 12, 18, and 24 months, with interim telephone study visits. Hormone usage and adherence, coagulation parameters, thrombophilia polymorphisms, and platelet activation will be assessed. In Aim 2, well-established qualitative and survey research methods will be used. Up to 20 adult and pediatric hematologists will complete individual interviews. Data from these interviews will be used to generate items for a new survey that will undergo survey development methods (cognitive interviews, pilot testing) before being fielded to a sample of U.S. and Canadian hematologists to understand their attitudes, behaviors, and intentions to recommend thromboprophylaxis to transgender youth at risk for thrombosis and factors associated with these intentions. The results of this work provide the foundation for 1) an intervention targeting physicians to improve knowledge of thrombosis risk in the setting of GAHT and 2) development of clinical guidance to aid in referral, evaluation, and management of transgender youth at risk for thrombosis.

PROJECT NARRATIVE

The proposed research is relevant to public health because understanding changes in coagulation factors that might increase the risk of a blood clot among transgender and gender nonconforming adolescents and young adults who are using estrogen for gender-affirming hormone therapy is important for physicians counseling transgender people about the risks of a blood clot, and for patients and their families to be able to make informed decisions about their health care. This research will also provide information about which youth with other risk factors for a blood clot should be evaluated and perhaps start anticoagulation before starting gender-affirming hormone therapy. Overall, the information that is learned from this work is important to the development of tools for both gender care clinicians and hematologists in order to standardize clinical practice, reduce health care inequalities, and improve the overall health of transgender and gender nonconforming adolescents and young adults.

FACILITIES AND OTHER RESOURCES

Environment: Contribution to Success

Dr. Tanya Mullins's primary appointment is through Cincinnati Children's Hospital Medical Center (CCHMC), and she is an affiliated faculty member of the University of Cincinnati (UC) College of Medicine. Dr. Tanya Mullins joined the faculty in 2010 and is currently an Associate Professor of Pediatrics. She has successfully led research teams both locally with faculty at CCHMC ((b)(6) , University of Cincinnati College of Medicine (including (b)(6) who served as a key mentor on Dr. Mullins's K23), and nationally with faculty across the U.S. for both her NIH K23 and NIH Adolescent Trials Network for HIV/AIDS Interventions work. Dr. Tanya Mullins has an established collaboration with (b)(6) (co-investigator) through their prior work examining risk of thrombosis in transgender youth receiving gender-affirming hormone therapy (described below), as well as co-authoring several clinical reviews and co-presenting invited workshops at national/international meetings on the topic of abnormal uterine bleeding in adolescents. Dr. Tanya Mullins has also collaborated with (b)(6) (collaborator for this proposal) on a clinical manuscript. Dr. Tanya Mullins, (b)(6) and (b)(6) are all housed within the Division of Adolescent and Transition Medicine at CCHMC, with offices (b)(6)

(b)(6) 's primary appointment also is through Cincinnati Children's Hospital Medical Center (CCHMC), and he is an affiliated faculty member of the University of Cincinnati (UC) College of Medicine. (b)(6) is an Associate Professor of Pediatrics. His laboratory currently occupies a (b)(6) wet-laboratory space. (b)(6) (b)(6) s laboratory is an additional (b)(6) laboratory used as a tissue room and chemical/radioisotope use room, which is shared with (b)(6) The dedicated and shared laboratory space includes all the necessary equipment for state-of-the-art molecular biology and biochemistry. Facilities (b)(6) include cold rooms, darkrooms, a radioisotope laboratory, common equipment rooms, tissue processing/sectioning rooms, light and fluorescence microscopy rooms, confocal facilities, transgenic core, DNA sequencing core, Pathology Research core, chip array core, and dishwashing and autoclaving rooms. The research of (b)(6) laboratories is heavily weighted toward understanding the molecular biology of hemostasis and platelet biology. (b)(6) 's office is (b)(6) (b)(6) a key collaborator for this proposal. (b)(6) and (b)(6) s laboratory spaces (b)(6)

Dr. Tanya Mullins and (b)(6) have an established collaboration with (b)(6) of the Transgender Health Clinic at CCHMC. Together, they completed one of the only studies focusing on the risk of thrombosis among transgender youth,[6] which serves as the foundation for the current proposal. All 3 physicians are (b)(6) whose goal is to develop and conduct cutting-edge collaborative research that will improve the care of transgender youth. This Collaborative will be utilized for recruiting physicians for the Aim 2 study of this proposal. Drs. Tanya Mullins and (b)(6) (b)(6) are both faculty in the Division of Adolescent and Transition Medicine and have worked closely together since (b)(6) In her role as the Associate Division Director for Research for the Division of Adolescent and Transition Medicine, Dr. Tanya Mullins collaborates closely with (b)(6) to review and monitor all research conducted in the Transgender Health Clinic.

As faculty members at CCHMC, Dr. Tanya Mullins and (b)(6) have access to support available through the joint CCHMC and UC Center for Clinical and Translational Science and Training (CCTST), funded in part by an institutional Clinical and Translational Science Award (CTSA). CCHMC provides numerous opportunities for faculty to interact with one another at the institution, through regularly scheduled research-in-progress presentations, research faculty cross talk, and department faculty meetings. With over 700 full time faculty within the Department of Pediatrics, there are an abundance of available intellectual resources.

Cincinnati Children's Hospital Medical Center (CCHMC) Overview

Founded in 1883, Cincinnati Children's Hospital Medical Center (CCHMC) is a non-profit hospital and research center pioneering breakthrough treatments, providing outstanding family-centered patient care, and training healthcare professionals for the future. It is a free-standing children's hospital that houses the Department of Pediatrics for the University of Cincinnati (UC) College of Medicine. This 670-bed hospital serves as the UC College of Medicine academic health center's major teaching facility for pediatrics and is the only children's hospital in the Cincinnati metropolitan area (population 2.2 million). In FY2020, CCHMC had nearly 1.3 million

patient encounters, including over 155,000 Emergency Department and Urgent Care visits and 1.08 million outpatient encounters. While focused on providing primary, tertiary, and quaternary care for the population in the local tri-state area, patients have come from 51 countries and all 50 states, as well as Washington, DC, and Puerto Rico. In 2021-2022, CCHMC was ranked as the 4th top pediatric hospital by the U.S. News & World Report. In 2019, CCHMC was ranked third among children's hospitals in number of research grants and NIH awards. This rich clinical and research environment offers numerous opportunities for investigators.

Research at CCHMC

William Cooper Procter, a benefactor of the hospital, established the Cincinnati Children's Research Foundation (CCRF) with an endowment and a building devoted to research in children's diseases that opened in 1931. The CCRF is the administrative and organizational entity for CCHMC's pediatric research mission. The CCRF includes all 41 divisions—six of which are basic research divisions—within the Department of Pediatrics. In 2020, $215 million in grants and contracts was awarded to the institution, including National Institutes of Health (NIH) funding of $159.3 million (direct and indirect costs). Furthermore, the research endowment supports CCRF scientific training, infrastructure, and Shared "Core" Facilities at CCHMC. The CCRF manages 1.4 million square feet of research space. The newest research tower, the "Clinical Sciences Pavilion" (also known as the "Location T") opened in June 2015. The CCRF includes multiple departments focused on enhancing research and research compliance, housing the Center for Clinical and Translational Science and Training (CCTST); Center for Technology Commercialization; Office for Clinical and Translational Research; Office of Research Compliance and Regulatory Affairs (ORCRA); and Sponsored Programs Office (SPO).

CCHMC received accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in 2007. ORCRA and SPO offer a number of educational opportunities, including sessions addressing informed consent, writing clinical study protocols, grant budgetary management, and institutional review board (IRB) issues. Research is further supported by division assignment to a dedicated institutional review board liaison ("research compliance specialist") who assists with efficiently developing and modifying protocols to facilitate research, while maintaining strict protection of human subjects. These specialists pre-review IRB protocols which allows for clarification and corrections prior to full-board review. The IRB further streamlines the submission and review process by utilizing an electronic submission process. The IRB regularly partners with the IRBs of other institutions for multisite studies.

Division of Adolescent and Transition Medicine

Dr. Tanya Mullins, (b)(6) (collaborator), and (b)(6) (collaborator) have appointments in the Division of Adolescent and Transition Medicine at CCHMC. The Division had over 11,000 outpatient encounters in FY2020. With 12 full time faculty, the Division is a national leader in research, primary and consultative clinical care, and education in adolescent health. The Teen Health Center is one of the greatest assets of the Division. The Teen Health Center is a primary and referral clinic located within CCHMC, serving adolescents 12-25 years of age. The *Transgender Health Clinic* is housed within the Teen Health Center, providing gender care for youth up to age 25 years and from a four-state catchment area (Ohio, Kentucky, Indiana, West Virginia). For the last 3 years, approximately 300 new patients were seen in the Transgender Health Clinic per year. For the proposed study, transgender and gender nonconforming patients who are starting estradiol for gender-affirming hormone therapy will be recruited from the Transgender Health Clinic. Research participants are routinely recruited from this clinic, and patients and families have historically been eager to participate in research studies. The division is structured to support academic faculty in pursuing research. In FY2021, Division faculty received over $1.5 million direct grant funding. The Division's business director has experience in grants management, and the Division houses administrative expertise in grant submission and support. Dr. Tanya Mullins serves as the Division's research director (since 2018) and oversees the administration and strategic planning for the overall research within the Division. Division faculty have access to site licenses for major statistical packages, including STATA and SAS, through CCHMC.

Cancer and Blood Diseases Institute

(b)(6) **and** (b)(6) are appointed as faculty in the Cancer and Blood Institute (CBDI) at CCHMC. CBDI houses the Divisions of Experimental Hematology and Cancer Biology, Bone Marrow Transplantation, Oncology, and Hematology. Scientific programs within the CBDI include: i) Stem Cell Biology; ii) Molecular and Gene Therapy; iii) Cell Signaling; iv) Leukemia Biology, v) Cancer Pathology and Cancer Biology, and vi) Hemostasis and Thrombosis. Grant funding for CBDI in fiscal year 2020 was $25.7 million, with an additional

$3.5 million in funding from industry. There are regular interactions between the scientists and the clinicians in the CBDI in the form of weekly Floor Meetings, Data Blitz, and grant presentation meetings. In addition, monthly seminars and a faculty cross talk are held. Twice a year, a formal translational retreat is organized featuring both clinical and basic science researchers presenting on the same topic. There is strong institutional support for travel, books, journals, manuscript preparation, and continuing education. Faculty also benefit from state-of-the-art Cincinnati Children's Research Foundation core facilities. This includes the Flow Cytometry Core (see below) with 2 dedicated cell sorters and multi-color fluorescent-activated cell sorters (FACS) analyzers as well as dedicated expert personnel. The Division of Hematology is home to the Hemostasis and Thrombosis Laboratory, the specialty clinical coagulation laboratory for CCHMC. (b)(6) has had a long-standing clinical collaboration with the Hemostasis and Thrombosis Laboratory and has worked with them on multiple research manuscripts.[29,74,78,201-204] This existing collaboration will facilitate the proposed research.

Division of Biostatistics and Epidemiology

(b)(6) (collaborator/biostatistician) holds an appointment in the Division of Biostatistics and Epidemiology and is a Professor in the Department of Pediatrics. This Division specializes in the design, data management, and statistical analysis of randomized controlled trials, observational studies, clinical studies, quality control initiatives, and translational research. Members of the Division conduct innovative research and engage in multidisciplinary research projects with basic research and clinical divisions of CCHMC. The Division also provides education, training, and consultation to students and professionals at CCHMC, University of Cincinnati, the local Veteran's Administration hospital organization, and in the community. The Division houses 21 faculty and more than 50 staff with expertise in numerous statistical and epidemiological methods who partner with nearly all of the clinical and translational research programs of CCHMC. The Division is currently engaged in collaborative, independent, and industry grants totaling $13.9 million in FY2020.

Institutional Support

CCHMC has a strong history of supporting investigators and has numerous resources for clinical and other researchers. CCHMC provides opportunities for fiscal support of research projects, including offering several internal grants. Dr. Tanya Mullins has successfully competed for these internal funding opportunities, including the Procter Scholar Award and the Place Outcomes Research Award. Career development opportunities for faculty at all levels are available through the Office of Academic Affairs and Career Development. This office is (b)(6), who served as (b)(6) on Dr. Tanya Mullins's K23 award and also serves as (b)(6) for the Division of Adolescent and Transition Medicine. This Office presents monthly seminars on a variety of topics, including grantsmanship, mentoring, and research integrity. All of these seminars are recorded and archived; thus, they are always available for reference. CCHMC is also committed to the career development of women faculty through the Charlotte R. Schmidlapp Center for Career Development of Women in Academic Pediatrics. This Center, which began in 1998, is dedicated to providing mentorship to women in order to facilitate overall career development.

Physical Resources

Computing Resources: All research staff have their own individual laptop computer, with word processing, data presentation, bibliographic, and statistical programs. The laptops are capable of accessing the CCHMC network from home or while traveling and can be used during recruitment of participants and during study visits. Computers are replaced every three years with an upgraded model by CCHMC at no cost. All computers are networked to CCHMC's secure intranet and, via a firewall, to the internet. All Microsoft Windows and Linux servers are backed up with daily incremental backups, weekly full backups, and monthly offsite vaults as needed.

Office/Work Space: The Division of Adolescent and Transition Medicine offices have (b)(6) of space. Dr. Tanya Mullins has her own private office (b)(6) (b)(6). All offices (b)(6) (b)(6) Dr. Tanya Mullins's research coordinator, (b)(6) has a desk (b)(6) (b)(6)

Administrative Support: Dr. Tanya Mullins has dedicated administrative support (effort).

EFFORT

Research Flow Cytometry Core

The Research Flow Cytometry Core will be used for evaluation of platelet activation with initiation of GAHT. (b)(6) (collaborator) has had significant experience with flow cytometric analysis of platelet activation and with the Research Flow Cytometry Core, having conducted studies using this Core.

The Research Flow Cytometry Core at CCHMC provides state-of-the-art instrumentation, services, training and education for single cell analysis. The Research Flow Cytometry Core is accessible to research investigators, graduate students, and technicians of CCHMC and the University of Cincinnati College of Medicine. The Research Flow Cytometry Core resides (b)(6)
(b)(6)

The Research Flow Cytometry Core has 6.5 full time employees who operate and train investigators in the use of 8 analytical cytometers, 5 cell sorters, and an imaging cytometer, in addition to providing multiplexed and traditional enzyme-linked immunosorbent assay (ELISA) services. The analytical cytometers (1 LSRII, 3 LSR Fortessa's, and 1 Aurora [each with 5 lasers] and 3 FACSCanto's [each with 3 lasers]) are equipped for analysis of up to 40 fluorochromes. The imaging cytometer is equipped with 3 lasers and can detect up to 10 fluorochromes. Five high-speed cell sorters (2 FACSAriaII's, 1 SH800S, 1 MA900 and 1 MoFloXDP) are maintained by Research Flow Cytometry Core staff. FACSAriaII's and MoFloXDP are operated by staff (b)(6)
(b)(6) The SH800S and the MA900 are available 24/7 as user-operated for investigators, students, and technicians who have been trained by RFCC staff. In addition, all cell sorters are housed in biosafety cabinets for sorting of infectious samples under heightened BSL2 conditions.

Other Intellectual Resources

The CCHMC *Division of Biomedical Informatics* supports the Biomedical Informatics Core of the joint UC College of Medicine and CCHMC Center for Clinical and Translational Science and Training (CCTST), which is funded in part by an institutional Clinical and Translational Science Award (CTSA). The Biomedical Informatics Core supports researchers with resources such as data storage systems, database servers, collaboration tools, and an inventory of research software applications. It also offers assistance with data management, clinical trial design and management, and bioinformatics queries. **The Research Electronic Data Capture (REDCap) is a software toolset and workflow methodology that will be used to manage study data in both aims and for survey administration in Aim 2.** The resulting product is a secure, HIPAA-capable web-based data management tool that is flexible enough to be used for any type of research, provides an intuitive interface for users to enter validated data, and offers an export mechanism for export of data to common statistical packages. It is provided **free of charge** for CCHMC investigators by the CCTST.

In addition to the Biomedical Informatics Core, the CCTST coordinates a wide range of other services. The *Biostatistics, Epidemiology, and Research Design (BERD)* program provides CCHMC and UC researchers with rapid access to assistance with research methods. Researchers are matched to BERD faculty by the needs of the researcher. Services provided by the BERD program include protocol or manuscript review, assistance with IRB protocol preparation, biostatistical guidance, assistance with power calculations, creation of data collection instruments, and consultation on research ethics. The *Regulatory Knowledge and Support* program supports best practices in human subjects protection and aids researchers in maintaining regulatory compliance. Finally, *Research Central* facilitates access to clinical research resources for faculty and trainees.

The *Pratt Library* at CCHMC is the primary resource for journal and reference book materials. The library maintains access to numerous electronic journals and other resources, which are available from any computer terminal within CCHMC and via internet connections outside the facility. The UC College of Medicine library's electronic resources are also easily available to CCHMC faculty. The library itself is located within walking distance and provides access to numerous electronic search engines and online journals, as well as in-print books. Both libraries provide training courses for faculty, including seminars on use of electronic databases and bibliographic software.

EQUIPMENT

No equipment meeting the NIH definition ("nonexpendable personal property having a useful life of more than one year and an acquisition cost of $5,000 or more per unit") will be needed for this study. Standard laboratory equipment such as centrifuges, chemical hoods, laminar flow hoods, refrigerators (4ºC), and freezers (-20ºC) are available within (b)(6)'s laboratory. In addition to the standard laboratory equipment, (b)(6)'s lab has the following pieces of equipment that are key for completion of the proposed studies.

Freezer (-80ºC)

(b)(6)'s laboratory has a -80ºC freezer with adequate space for storage of aliquoted samples until they are ready to be processed in a batched fashion. Further, there is adequate space for long-term storage of samples for the biologic repository of plasma and genomic DNA.

Plate Reader

(b)(6)'s laboratory has a BioTek plate reader with absorbance, fluorescence, and luminescence capabilities that are adequate for the proposed ELISA studies and chromogenic coagulation factor assays.

Quantitative PCR System

(b)(6)'s laboratory has a Bio-Rad RT-PCR system that is compatible with the proposed methodology of determination of pro-thrombotic genetic polymorphisms (factor V Leiden and prothrombin G20210A polymorphisms).

Thrombin Generation

For assessment of thrombin generation, the (b)(6) laboratory has a Diagnostica Stago Thrombinoscope for thrombin generation assays. The (b)(6) laboratory has experience with both human and murine samples for thrombin generation assays.

Core Equipment

The platelet studies, led by (b)(6) and (b)(6) (collaborator), will make use of the Research Flow Cytometry Core (RFCC) at CCHMC. The RFCC has 6.5 full time employees who operate and train investigators in the use of 8 analytical cytometers, 5 cell sorters and an imaging cytometer in addition to providing multiplexed and traditional ELISA services. The analytical cytometers (1 LSRII, 3 LSR Fortessa's, and 1 Aurora, each with 5 lasers and 3 FACSCanto's, each with 3 lasers) are equipped for analysis of up to 40 fluorochromes. The imaging cytometer is equipped with 3 lasers and can detect up to 10 fluorochromes. Five high-speed cell sorters (2 FACSAriaII's; 1 SH800S, 1 MA900 and 1 MoFloXDP) are maintained by RFCC staff. FACSAriaII's and MoFloXDP are operated by Core staff from 8:30 AM to 6:00 PM. Off-hour sorts are available on the FACSAriaII's. The SH800S, and the MA900 are available 24/7 as user-operated for investigators, students, and technicians who have been trained by RFCC staff. In addition, all cell sorters are housed in biosafety cabinets for sorting of infectious samples under heightened BSL2 conditions.

Hemostasis-Thrombosis Laboratory

The Hemostasis-Thrombosis Laboratory in the Division of Hematology, Cancer, and Blood Diseases Institute has 2 Stago STA-R-Max systems for high-throughput coagulation testing. This includes testing for the proposed studies, including von Willebrand Factor, free and total protein S, and protein C activity.

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix:	First Name*: Tanya	Middle Name Lilliane Kowalczyk	Last Name*: Mullins	Suffix:

Position/Title*:	ASSOCIATE PROFESSOR
Organization Name*:	Children's Hospital Medical Center
Department:	Pediatrics
Division:	Adolescent and Transition Med
Street1*:	3333 Burnet Avenue
Street2:	(b)(6)
City*:	Cincinnati
County:	Hamilton
State*:	OH: Ohio
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	452290000

Phone Number*:	(b)(6)	Fax Number:	(b)(6)
E-Mail*:	(b)(6)		

Credential, e.g., agency login:	(b)(6)
Project Role*: PD/PI	Other Project Role Category:
Degree Type: MD, MS	Degree Year:
Attach Biographical Sketch*: File Name:	Mullins_T_Biosketch.pdf
Attach Current & Pending Support: File Name:	

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

PROFILE - Senior/Key Person

Prefix: First Name*: (b)(6) Middle Name Last Name*: (b)(6) Suffix:

Position/Title*: ASSOCIATE PROFESSOR
Organization Name*: Children's Hospital Medical Center
Department: Pediatrics
Division: Hematology
Street1*: 3333 Burnet Avenue
Street2:
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 452290000

Phone Number*: (b)(6) Fax Number:
E-Mail*: (b)(6)

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year:

Attach Biographical Sketch*: File Name: (b)(6)_Biosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: (b)(6) Middle Name Last Name*: (b)(6) Suffix:

Position/Title*: PROFESSOR-FACULTY
Organization Name*: Children's Hospital Medical Center
Department: Pediatrics
Division: Adolescent and Transition Med
Street1*: 3333 Burnet Avenue
Street2: (b)(6)
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 452290000

Phone Number*: (b)(6) Fax Number: (b)(6)
E-Mail*: (b)(6)

Credential, e.g., agency login: eRA Commons User Name

Project Role*: Other (Specify) Other Project Role Category: Collaborator

Degree Type: MD Degree Year:

Attach Biographical Sketch*: File Name: (b)(6)_Biosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: (b)(6) Middle Name Last Name*: (b)(6) Suffix:

Position/Title*: ASSOCIATE PROFESSOR
Organization Name*: Children's Hospital Medical Center
Department: Pediatrics
Division: Adolescent and Transition Med
Street1*: 3333 Burnet Avenue
Street2: (b)(6)
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 452290000

Phone Number*: (b)(6) Fax Number: (b)(6)
E-Mail*: (b)(6)
Credential, e.g., agency login: eRA Commons User Name
Project Role*: Other (Specify) Other Project Role Category: Collaborator
Degree Type: DO, RPh, MPH Degree Year:
Attach Biographical Sketch*: File Name: (b)(6)_Biosketch.pdf
Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: (b)(6) Middle Name Last Name*: (b)(6) Suffix:

Position/Title*: ASSISTANT PROFESSOR
Organization Name*: Children's Hospital Medical Center
Department: Pediatrics
Division: Experimental Hematology
Street1*: 3333 Burnet Avenue
Street2:
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 452290000

Phone Number*: (b)(6) Fax Number:
E-Mail*: (b)(6)
Credential, e.g., agency login: eRA Commons User Name
Project Role*: Other (Specify) Other Project Role Category: Collaborator
Degree Type: Degree Year: PhD
Attach Biographical Sketch*: File Name: (b)(6) Biosketch.pdf
Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: (b)(6) Middle Name Last Name*: (b)(6) Suffix:

Position/Title*: PROFESSOR-FACULTY
Organization Name*: Children's Hospital Medical Center
Department: Pediatrics
Division: Biostatistics & Epidemiology
Street1*: 3333 Burnet Avenue
Street2:
City*: Cincinnati
County: Hamilton
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 452290000

Phone Number*: (b)(6) Fax Number:
E-Mail*: (b)(6)

Credential, e.g., agency login: eRA Commons User Name

Project Role*: Other (Specify) Other Project Role Category: Biostatistician

Degree Type: PhD Degree Year:

Attach Biographical Sketch*: File Name: (b)(6) .Biosketch.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02/28/2023)

BIOGRAPHICAL SKETCH

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

NAME: Mullins, Tanya Lilliane Kowalczyk

eRA COMMONS USER NAME (credential, e.g., agency login): (b)(6)

POSITION TITLE: Associate Professor of Pediatrics

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Winthrop University, Rock Hill, SC	BS	05/1997	Biology; Honors
Medical University of South Carolina, Charleston, SC	MD	05/2001	Medicine
Vanderbilt Children's Hospital, Nashville, TN	Resident	06/2004	Pediatrics
Cincinnati Children's Hospital Medical Center, Cincinnati, OH	Fellow	06/2007	Adolescent Medicine
University of Cincinnati, Cincinnati, OH	MS	06/2008	Epidemiology/Clinical Research
Cincinnati Children's Hospital Medical Center, Cincinnati, OH	Fellow	06/2010	NRSA Research Fellow

A. Personal Statement

I am an Associate Professor of Pediatrics at Cincinnati Children's Hospital Medical Center, an Adolescent Medicine-trained physician, and a physician-scientist. Following my clinical fellowship, I completed a separate three-year National Research Service Award (NRSA) research fellowship to further develop my skills. My primary research interest is optimizing the health of adolescents and young adults, including transgender youth. My research program has focused on biomedical prevention of human immunodeficiency virus (HIV) through increasing uptake of rapid HIV testing by youth and the use of microbicides and oral pre-exposure prophylaxis (PrEP). Through my work with PrEP and as an adolescent medicine specialist, I also provide clinical care to transgender youth. More recently my research has expanded to include studies focused on transgender youth, including a recently completed study examining thrombosis risk and occurrence in transgender youth. This work was presented at the American Society of Hematology (ASH) 2020 meeting and highlighted by an ASH-hosted "poster walk-through." A manuscript detailing these findings – co-authored by (b)(6) and me – was published in *Pediatrics* in 2021 and serves as the basis for the proposed study.

My formal and experiential training and ongoing research provide the expertise necessary to lead and conduct the proposed work. During my training, I gained experience in qualitative and survey analysis through my work on human papillomavirus vaccination with (b)(6) My research program in HIV prevention has used both qualitative and quantitative research methods to examine adolescent HIV testing attitudes and behaviors and attitudes of HIV-care providers toward use of oral pre-exposure prophylaxis (PrEP) for HIV prevention in youth (Protocol Chair, Adolescent Trials Network for HIV/AIDS Interventions [ATN]). I also served as an ATN Protocol Chair leading a follow-up qualitative study examining the impact of participating in a PrEP demonstration project on clinician attitudes toward use of PrEP in adolescents. I led a regional research team during my NIH (NICHD) K23 Career Development Award, which used qualitative and quantitative methods to examine the attitudes of primary care physicians toward the use of biomedical HIV prevention agents - topical microbicides and oral PrEP - in youth. I have training and expertise in qualitative and quantitative research methods, survey development and methods, and data analysis, including formal training as detailed below in "Other Experience and Professional Memberships".

Given my research and team leadership experience, I am well-suited to serve as the PI for the proposed project. My training and work as a board-certified adolescent medicine physician provide the skills to understand the care of transgender youth. I have experience leading studies that have recruited both adolescents/young adults and physicians. My methodologic expertise in qualitative and survey research methods, as well as my proven record in leading successful clinical research studies, is crucial to the proposed project. The proposed research team has a history of successful collaboration between the PI, co-I, and the Director of the Transgender Program at Cincinnati Children's Hospital Medical Center. Further, in my roles as the Director of Research and now Associate Division Director for Research for the Division of Adolescent and Transition Medicine, (b)(6) and I have worked extensively together to supervise research within the Transgender Health Clinic. Through my expertise and my experience leading research teams, I am well-positioned to successfully serve as PI for this proposed work.

Ongoing and recently completed projects that I would like to highlight include:

(b)(4); (b)(6)
Mullins (PI)
01/01/19 – 12/31/20 (NCE to 5/31/21)
Integrating Biomedical Human Immunodeficiency Virus (HIV) Prevention into HIV Care

(b)(4); (b)(6)
Mullins (PI)
08/08/19 – 08/07/20
Attitudes of Adults Seeking Treatment for Opioid Use Disorder toward HIV Pre-Exposure Prophylaxis (PrEP)

(b)(4); (b)(6)
(b)(6)
08/01/16 – 07/31/19
Parent Project: Innovation in Transgender Service Delivery
Mullins (Sub-project PI)
02/01/19 – 07/31/19
Sub-Project: Thrombosis Risk of Gender-Affirming Hormone Therapy in Adolescent and Young Adult Transgender People

NIH K23 HD072807
Mullins (PI)
09/19/13 – 08/31/18 (NCE to 12/31/18)
Physician Attitudes toward New Biomedical HIV Prevention Interventions in Youth

a. Mullins ES, Geer R, Metcalf M, Piccola J, Lane A, Conard LA, and **Mullins TLK**. Risk factors for and occurrence of thrombosis in transgender adolescents and young adults receiving gender-affirming hormone therapy. *Pediatrics*. 2021. 147(4):e 2020023549. PMID: 33753543.
b. **Mullins TL**, Zimet G, Lally M, Kahn JA, and Adolescent Medicine Trials Network for HIV/AIDS Interventions. Adolescent HIV care providers' attitudes toward the use of oral pre-exposure prophylaxis (PrEP) in youth. *AIDS Patient Care STDs*. 2016. 30(7):339-48. PMCID: PMC4948218.
c. **Mullins TLK**, Zimet GD, Lally M, Xu J, Thornton S, Kahn JA, and the Adolescent Medicine Trials Network for HIV/AIDS Interventions. HIV care providers' intentions to prescribe and actual prescription of pre-exposure prophylaxis (PrEP) to at-risk adolescents and adults. *AIDS Patient Care STDs*. 2017. 31(12): 504-516. PMCID: PMC5724583.
d. **Mullins TLK**, Idoine CR, Zimet GD, and Kahn JA. Primary care physician attitudes and intentions toward use of HIV pre-exposure prophylaxis in adolescents in one metropolitan region. *J Adolesc Health*. 2019. 64(5):581-588. PMCID: PMC6478546.

B. Positions and Honors

Positions and Employment

2021- Associate Division Director for Research, Division of Adolescent and Transition Medicine, Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH

2018 - 2021	Director of Research, Division of Adolescent and Transition Medicine, CCHMC, Cincinnati, OH
2018 - 2019	Director of Transgender Program Research, Division of Adolescent and Transition Medicine, CCHMC, Cincinnati, OH
2016 -	Associate Professor of Clinical Pediatrics, Division of Adolescent and Transition Medicine, CCHMC, Cincinnati, OH
2010 - 2016	Assistant Professor of Pediatrics, Division of Adolescent and Transition Medicine, CCHMC, Cincinnati, OH
2007 - 2010	Staff Physician, Division of Adolescent Medicine, CCHMC, Cincinnati, OH

Other Experience and Professional Memberships

2018	Participant, NIH Office of Behavioral and Social Science Research 18th Annual Summer Institute on Randomized Behavioral Clinical Trials, Warrenton, VA (competitive application)
2018 -	Elected member, Society for Pediatric Research
2016 -	Secretary-Treasurer, Society for Adolescent Health and Medicine
2015 - 2016	Deputy Secretary-Treasurer, Society for Adolescent Health and Medicine
2015	Invited Participant, UNICEF "Consultation on Clinical and Operational Considerations for the Implementation of Pre-Exposure Prophylaxis (PrEP) in Sexually Active Older Adolescents (15-19 years old)," Vancouver, BC, Canada
2015	Instrumentation: Development, Testing, and Revision, University of North Carolina-Chapel Hill
2015	Writing Questions for Surveys, Joint Program in Survey Methodology, Washington, D.C.
2014	Qualitative Data Analysis Workshop, University of North Carolina-Chapel Hill, NC
2014	Cognitive Interviewing Workshop, Joint Program in Survey Methodology, Washington, D.C.
2010 - 2014	President, Ohio Valley Chapter, Society for Adolescent Health and Medicine
2009	Semi-structured Interviewing and Mixed Methods Research, Summer Institute in Survey Research Techniques, University of Michigan, Ann Arbor, MI
2008 -	American Board of Pediatrics: Adolescent Medicine certification
2006 - 2010	Secretary-Treasurer, Ohio Valley Chapter, Society for Adolescent Health and Medicine
2005 -	Member, Ohio Valley Chapter, Society for Adolescent Health and Medicine
2005 –	Member, Society for Adolescent Health and Medicine
2004 -	American Board of Pediatrics: General Pediatrics certification
2001 -	Member, American Academy of Pediatrics
2000 -	Member, Alpha Omega Alpha Medical Honor Society
1995 -	Member, Phi Kappa Phi Honor Society

Honors

2019	Mid-Career Women Faculty Professional Development Seminar, Association of American Medical Colleges (AAMC) (national competitive career development program)
2016	Awarded Fellow Status, Society for Adolescent Health and Medicine, for commitment and contributions to the health and welfare of adolescents
2013	Early Career Women Faculty Professional Development Seminar, Association of American Medical Colleges (AAMC) (competitive application)
2010-2013	Procter Scholar Award, Cincinnati Children's Hospital Medical Center (competitive award for junior faculty that provides protected time for research)
2005	Clinical Research Fellowship for Tuition Support, Cincinnati Children's Hospital Medical Center
2001	Merck Pharmaceutical Company Award, Medical University of South Carolina
2001	Janet M. Glasgow Memorial Achievement Citation, American Medical Women's Association/Medical University of South Carolina
2000	Elected to Alpha Omega Alpha Medical Honor Society, Medical University of South Carolina

C. Contributions to Science

1. Thrombosis Risk Factors and Occurrence among Transgender Youth using Hormones

One critical potential risk of use of gender-affirming hormone therapy (GAHT) in transgender youth is the development of thrombosis. Studies among transgender adults demonstrate conflicting findings about this risk; most prior studies are also limited in their use of hormone regimens that are not available in the U.S. Our group conducted a retrospective review of data of over 600 youth ages 13-24 years-old using GAHT to examine risk

factors for thrombosis and occurrence of thrombosis. We found that many youth had both personal and family risk factors for thrombosis, and many youth had abnormal test results associated with increased risk of thrombosis, such as Factor VIII and plasminogen activator inhibitor-1 (PAI-1). However, none of the youth developed a clinically significant thrombosis. This study is the first study to examine thrombosis risk factors and occurrence in transgender youth. My specific roles were: study design and management, data collection, data cleaning, interpreting data analysis, preparation of abstract and manuscript.

a. Mullins ES, Geer R, Metcalf M, Piccola J, Lane A, Conard LA, and **Mullins TLK**. Risk factors for and occurrence of thrombosis in transgender adolescents and young adults receiving gender-affirming hormone therapy. *Pediatrics*. 2021. 147(4):e 2020023549. PMID: 33753543.

2. Clinician Attitudes and Behaviors toward Use of Biomedical HIV Prevention Methods in Youth

Our team was the first to publish work specifically examining the attitudes, intentions, and behaviors of clinicians who care for adolescents and young adults toward PrEP. I led two ATN-funded projects examining clinician attitudes and behaviors toward prescribing PrEP to youth. My K23 primary project consisted of interviewing physicians who provide primary care to adolescents to assess their attitudes and intentions toward use of biomedical HIV prevention methods, including PrEP, in youth; developing a new survey informed by the findings of the qualitative study; and fielding the survey to a national sample of 2500 U.S. physicians who care for adolescents. Our results were presented at multiple national and international meetings, including AIDS 2020. Additional manuscripts are in progress. Together, the findings from these studies are the bulk of the available data about the attitudes and intentions of clinicians who care for youth toward PrEP and demonstrate that minor-aged adolescents face unique barriers to PrEP, including parental barriers, barriers to legal confidential access to PrEP, and provider discomfort prescribing PrEP to minors. We also found that clinicians reported lower intention to prescribe HIV prevention methods to adolescents. Our findings are essential in designing interventions to increase clinician recommendation of PrEP and thus the overall success of PrEP as a prevention intervention among youth. My specific roles included: serving as protocol chair and leader for the ATN-funded studies (which included team members across the country) and PI on the K23 grant, conceptualizing and designing the studies, designing the interview guides, conducting interviews, survey development (including performing cognitive interviews and pilot testing), performing qualitative and quantitative data analysis, and drafting manuscripts and abstracts.

a. **Mullins TL**, Lally M, Zimet G, Kahn JA and the Adolescent Medicine Trials Network for HIV/AIDS Interventions. Clinician attitudes toward CDC interim pre-exposure prophylaxis (PrEP) guidance and operationalizing PrEP for adolescents. *AIDS Patient Care STDs*. 2015. 29(4):193-203. PMCID: PMC4378662.
b. **Mullins TL**, Zimet G, Lally M, Kahn JA, and Adolescent Medicine Trials Network for HIV/AIDS Interventions. Adolescent HIV care providers' attitudes toward the use of oral pre-exposure prophylaxis (PrEP) in youth. *AIDS Patient Care STDs*. 2016. 30(7):339-48. PMCID: PMC4948218.
c. **Mullins TLK**, Zimet GD, Lally M, Xu J, Thornton S, Kahn JA, and the Adolescent Medicine Trials Network for HIV/AIDS Interventions. HIV care providers' intentions to prescribe and actual prescription of pre-exposure prophylaxis (PrEP) to at-risk adolescents and adults. *AIDS Patient Care STDs*. 2017. 31(12): 504-516. PMCID: PMC5724583.
d. **Mullins TLK**, Idoine CR, Zimet GD, and Kahn JA. Primary care physician attitudes and intentions toward use of HIV pre-exposure prophylaxis in adolescents in one metropolitan region. *J Adolesc Health*. 2019. 64(5):581-588. PMCID: PMC6478546.

3. HIV Testing Among Adolescents

Because many people have never been tested for HIV and thus are unaware of their status, efforts to increase HIV testing among key populations, including adolescents, are critical. Because rapid HIV testing may be more acceptable to adolescents and thus increase uptake of HIV testing in this group, our team examined adolescent preferences for different HIV testing methods, the impact of test method on receipt of results, and the impact of offering rapid HIV testing on overall rates of testing. Half of youth agreed to HIV testing when offered their choice of testing method, and over 70% of youth chose a rapid method. Youth who chose a rapid method were significantly more likely to receive their results and received their results in a significantly shorter period of time as compared to youth who chose venipuncture testing. We also found that introducing rapid HIV testing into a clinical setting significantly increased overall rates of HIV testing in youth. This work provides evidence that offering youth their choice of interventions leads to greater uptake of prevention measures and supports the use of rapid testing methods among youth. My roles included: serving as PI and leading the

research team, conceptualizing and designing the studies, developing the survey, performing data analysis, and drafting abstracts and manuscripts.

a. **Kowalczyk Mullins T**, Braverman PK, Dorn LD, Kollar LK, and Kahn JA. Adolescent preferences for human immunodeficiency virus testing methods and impact of rapid tests on receipt of results. *J Adolesc Health*. 2010. 46(2):162-168. PMID: 20113922.
b. **Mullins TL**, Kollar LM, Lehmann C, and Kahn JA. Changes in human immunodeficiency virus testing rates among urban adolescents after introduction of routine and rapid testing. *Arch Pediatr Adolesc Med*. 2010. 164(9):870-874. PMID: 20819970.
c. **Mullins TK**, Braverman PK, Dorn LD, Kollar LK, and Kahn JA. Adolescent agreement to test for HIV when different methods are offered. *Int J STD AIDS*. 2012. 23:173-176. PMID:22581869.

4. Impact of Human Papillomavirus (HPV) Vaccination on Risk Perceptions and Behaviors

Although HPV vaccination is a prevention method that can significantly decrease morbidity and mortality related to HPV, vaccine uptake among girls has lagged behind expected uptake. Our team used survey and interview data originating from (b)(6) NIH-funded work to examine HPV vaccine-related risk perceptions among vaccinated girls. Overall, 13- to 21-year-old girls appropriately perceived themselves to be less at risk of HPV than other STIs immediately following vaccination, and the vast majority of girls continued to perceive a need for safer sexual behaviors. Over 30 months following initial vaccination, we found that 1) girls perceived themselves to be *more* at risk of STIs other than HPV, 2) perceived risk of STIs other than HPV was not associated with subsequent sexual behaviors or STI diagnosis, and 3) greater perceived need for safer sexual behaviors was associated with condom use at last sexual intercourse but not with other sexual behaviors or STI diagnosis. Interviews with 11- to 12 year-old girls demonstrated that most girls developed accurate risk perceptions about HPV but fewer developed accurate risk perceptions about other STIs by 30 months following vaccination; however, the vast majority of girls thought that safer sex was still important, regardless of their knowledge, risk perceptions, or sexual experience. Thus, our work provides reassuring evidence for parents and clinicians that risk perceptions among girls receiving the HPV vaccine are not associated with unsafe attitudes toward sex or riskier sexual behaviors. Such information can be incorporated into clinician recommendations about the HPV vaccine, which may lead to decreased vaccine hesitancy among parents and increased vaccine uptake. My specific roles in the project were: performing data analysis and interpretation and drafting or critically revising abstracts and manuscripts.

a. **Mullins TL**, Zimet GD, Rosenthal SL, Morrow C, Ding L, Shew ML, Fortenberry JD, Bernstein DI, and Kahn JA. Adolescent perceptions of risk and need for safer sexual behaviors after first human papillomavirus vaccination. *Arch Pediatr Adolesc Med.* 2012. 166 (1): 82-88. PMCID: PMC3708455.
b. Mayhew A, **Mullins TL,** Ding L, Rosenthal S, Zimet G, Morrow C, and Kahn JA. Risk perceptions and subsequent sexual behaviors after HPV vaccination in adolescents. *Pediatrics*. 2014. 133(3):404-11. PMCID: PMC3934341.
c. **Mullins TL**, Zimet GD, Rosenthal SL, Morrow C, Ding L, Huang D, and Kahn JA. Human papillomavirus vaccine-related risk perceptions and subsequent sexual behaviors and sexually transmitted infections among vaccinated adolescent women. *Vaccine*. 2016. 34(34):4040-5. PMCID: PMC4946413.
d. **Mullins TLK**, Rosenthal SL, Zimet GD, Ding L, Morrow C, Huang B, and Kahn JA. Human papillomavirus vaccine-related risk perceptions do not predict sexual initiation among young women over 30 months following vaccination. *J Adolesc Health*. 2018. 62(2): 164-169. PMCID: PMC5803391.

Full List of Published Works:

https://www.ncbi.nlm.nih.gov/sites/myncbi/tanya.mullins.2/bibliography/40275340/public/?sort=date&direction=ascending

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Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Children's Hospital Medical Center

Start Date*: 07-01-2022 **End Date*:** 06-30-2023 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Tanya	Lilliane Kowalczyk	Mullins		PD/PI	(b)(4); (b)(6)	(b)(6)			58,454.00	16,250.00	74,704.00
2.		(b)(6)				Collaborator					9,965.00	2,770.00	12,735.00
3.						Collaborator					5,683.00	1,580.00	7,263.00
4.						Co-Investigator					39,860.00	11,081.00	50,941.00
5.						Biostatistician					19,930.00	5,541.00	25,471.00

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **171,114.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Clinical Research Support	(b)(6)			63,187.00	17,566.00	80,753.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**80,753.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**251,867.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Organization: Children's Hospital Medical Center

Start Date*: 07-01-2022 **End Date*:** 06-30-2023 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,590.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**4,590.00**

E. Participant/Trainee Support Costs	Funds Requested ($)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 071284913
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Children's Hospital Medical Center

Start Date*: 07-01-2022 **End Date*:** 06-30-2023 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Internal Purchased Services	11,768.00
9 . Subject Incentives	10,500.00
10 . Other	4,642.00
Total Other Direct Costs	**26,910.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**283,367.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	59	283,367.00	167,187.00
		Total Indirect Costs	**167,187.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**450,554.00**

J. Fee	Funds Requested ($)*
	0.00

K. Total Costs and Fee	Funds Requested ($)*
	450,554.00

L. Budget Justification*	File Name: Budget_Justification_Update_11_04_21.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Children's Hospital Medical Center

Start Date*: 07-01-2023 **End Date*:** 06-30-2024 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Tanya	Lilliane Kowalczyk	Mullins		PD/PI	(b)(4); (b)(6)	(b)(6)			59,790.00	16,622.00	76,412.00
2.		(b)(6)				Collaborator					9,965.00	2,770.00	12,735.00
3.						Collaborator					5,853.00	1,627.00	7,480.00
4.						Co-Investigator					39,860.00	11,081.00	50,941.00
5.						Collaborator					5,730.00	1,593.00	7,323.00
6.						Biostatistician					19,930.00	5,541.00	25,471.00

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **180,362.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Clinical Research Support	(b)(6)			65,083.00	18,093.00	83,176.00
1	Research Support (Non-Clinical)				40,000.00	11,120.00	51,120.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**134,296.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**314,658.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Organization: Children's Hospital Medical Center

Start Date*: 07-01-2023 **End Date*:** 06-30-2024 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	6,210.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**6,210.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 071284913
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Children's Hospital Medical Center

Start Date*: 07-01-2023 **End Date*:** 06-30-2024 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	1,500.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Internal Purchased Services	59,634.00
9 . Subject Incentives	15,725.00
10 . Other	791.00
Total Other Direct Costs	**77,650.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**398,518.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	59	398,518.00	235,126.00
		Total Indirect Costs	**235,126.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**633,644.00**

J. Fee	Funds Requested ($)*
	0.00

K. Total Costs and Fee	Funds Requested ($)*
	633,644.00

L. Budget Justification*	File Name: Budget_Justification_Update_11_04_21.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Children's Hospital Medical Center

Start Date*: 07-01-2024 **End Date*:** 06-30-2025 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Tanya	Lilliane Kowalczyk	Mullins		PD/PI	(b)(4); (b)(6)	(b)(6)			59,790.00	16,622.00	76,412.00
2.		(b)(6)				Collaborator					9,965.00	2,770.00	12,735.00
3.						Collaborator					5,979.00	1,662.00	7,641.00
4.						Co-Investigator					39,860.00	11,081.00	50,941.00
5.						Collaborator					5,902.00	1,641.00	7,543.00
6.						Biostatistician					19,930.00	5,541.00	25,471.00

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **180,743.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Clinical Research Support	(b)(6)			67,035.00	18,636.00	85,671.00
1	Research Support (Non-Clinical)				41,200.00	11,454.00	52,654.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**138,325.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**319,068.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Organization: Children's Hospital Medical Center

Start Date*: 07-01-2024 **End Date*:** 06-30-2025 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	7,526.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**7,526.00**

E. Participant/Trainee Support Costs	Funds Requested ($)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 071284913
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Children's Hospital Medical Center

Start Date*: 07-01-2024 **End Date*:** 06-30-2025 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Internal Purchased Services	61,351.00
9 . Subject Incentives	16,725.00
10 . Other	801.00
Total Other Direct Costs	**78,877.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**405,471.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	59	405,471.00	239,228.00
		Total Indirect Costs	**239,228.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**644,699.00**

J. Fee	Funds Requested ($)*
	0.00

K. Total Costs and Fee	Funds Requested ($)*
	644,699.00

L. Budget Justification*	File Name: Budget_Justification_Update_11_04_21.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Children's Hospital Medical Center

Start Date*: 07-01-2025 **End Date*:** 06-30-2026 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Tanya	Lilliane Kowalczyk	Mullins		PD/PI	(b)(4); (b)(6)	(b)(6)			59,790.00	16,622.00	76,412.00
2.		(b)(6)				Collaborator					5,979.00	1,662.00	7,641.00
3.						Co-Investigator					39,860.00	11,081.00	50,941.00
4.						Collaborator					6,079.00	1,690.00	7,769.00
5.						Biostatistician					19,930.00	5,541.00	25,471.00

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **168,234.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Clinical Research Support	(b)(6)			69,046.00	19,195.00	88,241.00
1	Research Support (Non-Clinical)				42,436.00	11,797.00	54,233.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**142,474.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**310,708.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Organization: Children's Hospital Medical Center

Start Date*: 07-01-2025 **End Date*:** 06-30-2026 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,960.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**4,960.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 071284913
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Children's Hospital Medical Center

Start Date*: 07-01-2025 **End Date*:** 06-30-2026 **Budget Period:** 4

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Internal Purchased Services	55,578.00
9 . Subject Incentives	17,525.00
10 . Other	2,204.00
Total Other Direct Costs	**75,307.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**390,975.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	59	390,975.00	230,675.00
		Total Indirect Costs	**230,675.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**621,650.00**

J. Fee	Funds Requested ($)*
	0.00

K. Total Costs and Fee	Funds Requested ($)*
	621,650.00

L. Budget Justification*	File Name: Budget_Justification_Update_11_04_21.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Children's Hospital Medical Center

Start Date*: 07-01-2026 **End Date*:** 06-30-2027 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Tanya	Lilliane Kowalczyk	Mullins		PD/PI	(b)(4); (b)(6)	(b)(6)			59,790.00	16,622.00	76,412.00
2.		(b)(6)				Collaborator					5,979.00	1,662.00	7,641.00
3.						Co-Investigator					39,860.00	11,081.00	50,941.00
4.						Collaborator					6,261.00	1,741.00	8,002.00
5.						Biostatistician					19,930.00	5,541.00	25,471.00

Total Funds Requested for all Senior Key Persons in the attached file **0.00**

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **168,467.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Clinical Research Support	(b)(6)			71,118.00	19,771.00	90,889.00
1	Research Support (Non-Clinical)				43,709.00	12,151.00	55,860.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**146,749.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**315,216.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 071284913

Budget Type*: ● Project ○ Subaward/Consortium

Organization: Children's Hospital Medical Center

Start Date*: 07-01-2026 **End Date*:** 06-30-2027 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	3,340.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**3,340.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 071284913
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Children's Hospital Medical Center

Start Date*: 07-01-2026 **End Date*:** 06-30-2027 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	1,500.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Internal Purchased Services	44,302.00
9 . Subject Incentives	2,550.00
Total Other Direct Costs	**48,352.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**366,908.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	59	366,908.00	216,476.00
		Total Indirect Costs	**216,476.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**583,384.00**

J. Fee	Funds Requested ($)*
	0.00

K. Total Costs and Fee	Funds Requested ($)*
	583,384.00

L. Budget Justification*	File Name: Budget_Justification_Update_11_04_21.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION: Children's Hospital Medical Center

Personnel: ($1,511,517)
A. Senior Key Personnel

Tanya L.K. Mullins, MD (Primary Investigator, (b)(6) Years 1-5): Dr. Tanya Mullins is an Associate Professor of Pediatrics in the Division of Adolescent and Transition Medicine at Cincinnati Children's Hospital Medical Center (CCHMC). Her prior research experience (funded by an NIH K23 and the NIH-funded Adolescent Trials Network for HIV/AIDS Interventions) demonstrates her ability to successfully lead research teams and programs to fruition. She will be the primary investigator of the proposal and will oversee all activities of the research. She will have overall responsibility for the scientific, regulatory, and administrative aspects of the proposed work. She has extensive experience in clinical research and clinical studies. She will lead the clinical studies in both aims of the proposal. She will be responsible for 1) planning and implementation of the research (along with (b)(6)); 2) direct oversight of the clinical research coordinator in charge of recruitment and retention activities for both aims; 3) conducting interviews, cognitive interviews, and pilot testing; 4) generating survey items, survey development and refinement; 5) analysis and interpretation of qualitative and cognitive interview data analysis; 6) interpretation of pilot test and survey data analyses; and 7) leading and coordinating presentation of results and manuscript preparation. Along with (b)(6) and (b)(6) she will participate in the analysis and interpretation of data generated from this research proposal.

(b)(6) **MD (Co-Investigator, (b)(6) Years 1-5):** (b)(6) is an Associate Professor of Pediatrics in the Division of Hematology, which is housed within the Cancer and Blood Diseases Institute at CCHMC. He will oversee the study visits for the first aim and all laboratory testing performed during Aim 1, particularly the laboratory testing. His laboratory will process all blood samples from the first aim and then distribute samples for the laboratory testing that is batched, with samples distributed to either the Hemostasis-Thrombosis Laboratory or the (b)(6) Laboratory (as detailed in "Approach"). He will train and directly oversee the Research Assistant hired for conducting the batched studies within his laboratory. As a pediatric hematologist, he will also review the results of the study tests and communicate clinically meaningful results to the transgender clinical care team. He also will consult on the qualitative and cognitive interviews conducted in the second aim. ***Please note that (b)(6) 's salary is over the current Executive Level II salary cap. Should the salary cap be adjusted at a later date, the salary charged to this project would be adjusted accordingly.***

(b)(6) **MD (Collaborator, (b)(6) Years 1-3):** (b)(6) is a Professor of Pediatrics in the Division of Adolescent and Transition Medicine at CCHMC. He will consult on sex hormone measurement and interpretation and on conduct of the longitudinal study in Aim 1. (b)(6) has expertise in both areas, as the local PI on the longstanding and productive "Breast Cancer and the Environment Research Program", a study of pubertal development of girls. (b)(6) will collaborate during the first 3 years of the research. (b)(6) has a partial appointment of (b)(6) at CCHMC. He will commit (b)(6) of his effort to this project for EFFORT ***Please note that (b)(6) 's salary is over the current Executive Level II salary cap. Should the salary cap be adjusted at a later date, the salary charged to this project would be adjusted accordingly.***

(b)(6) **PhD (Collaborator/Biostatistician, (b)(6) Years 1-5):** (b)(6) is an Associate Professor in the Division of Epidemiology and Biostatistics at CCHMC. He will collaborate on the statistical analysis of the data generated from Aims 1 and 2 of this research proposal. (b)(6) will assist with data management in the first 2 years of the proposal and will provide analytic support as study data are accumulated in the final 3 years of the project. ***Please note that (b)(6) 's salary is over the current Executive Level II salary cap. Should the salary cap be adjusted at a later date, the salary charged to this project would be adjusted accordingly.***

(b)(6) **PhD (Collaborator, (b)(6) Years 2-5):** (b)(6) is an Assistant Professor in the Division of Experimental Hematology and Cancer Biology, which is also housed within the Cancer and Blood Diseases Institute CCHMC. He has significant expertise in platelet biology, including differential platelet activation. He also has expertise in examining platelet activation via flow cytometry. Dr. (b)(6) will consult with (b)(6) in the execution and interpretation of the effect of estrogen on platelet

activation. (b)(6) will be involved for the last 4 years of the study during which the platelet studies will be conducted. His office is located adjacent to the office of (b)(6)

(b)(6) **RPh, DO, MPH (collaborator,** (b)(6) **Years 1-5):** (b)(6) is an Associate Professor of Pediatrics in the Division of Adolescent and Transition Medicine at CCHMC. She is the (b)(6) of the Transgender Health Center. (b)(6) the multidisciplinary team that cares for transgender youth at Cincinnati Children's Medical Center. (b)(6) will facilitate the recruitment of individuals starting estradiol gender-affirming hormone therapy and provide topical expertise.

B. Other Personnel

(b)(6) **BS (Clinical Research Coordinator [CRC] IV,** (b)(6) **Years 1-5):** (b)(6) (b)(6) is a CRC IV in the Division of Adolescent and Transition Medicine at CCHMC. She has worked with Dr. Tanya Mullins and (b)(6) on their interview, survey, and longitudinal studies. Through her work with Dr. Tanya Mullins, she has expertise recruiting both adolescents/young adults and physicians for research studies. Ms. (b)(6) has expertise with Research Electronic Data Capture (REDCap) survey software, as well as survey design, administration, and data management. Her experience thus makes her an ideal candidate to coordinate the studies from both Aim 1 and Aim 2. (b)(6) will assist with preparation and management of the institutional review board (IRB) protocol, management of the standard operating procedures manuals, performing recruitment/retention activities for participants in the studies in both aims, cleaning and coding interview and cognitive interview data, preparing and maintaining the study database, assisting with survey design, assisting with administration of pilot tests, leading survey dissemination, and assisting with manuscript preparation and other data dissemination activities. Dr. Tanya Mullins will directly oversee (b)(6) whose office space is located (b)(6)

TBD (Research Assistant II, (b)(6) **Years 2-5):** This research assistant (RA) will be a member of Dr. (b)(6) 's laboratory. This RA will be responsible for processing blood specimens, storage of plasma and DNA, delivery of specimens to the Hemostasis-Thrombosis Laboratory, and conducting assays within Dr. (b)(6) s lab. (b)(6) will be responsible for training and overseeing this RA.

Fringe Benefits: Children's Hospital Medical Center's fringe rate is based on our actual benefit costs. Over/under recoveries from actual costs are adjusted in current or future periods. The directly claimed fringe benefits are: FICA, Retirement, Worker's Compensation, Life Insurance, Unemployment Insurance, Disability Insurance, Health Insurance, Dental Insurance, Tuition Remission and the Employee Assistance Plan.

C, Travel: ($26,626)

1. Travel to Professional Meetings ($8,400 total, Years 3-5): In order to disseminate findings associated with the study, we request funds to attend 3 professional meetings (one each in Years 3, 4, and 5) at $2,800 each. This cost is based on the most recent costs for the PI associated with in-person attendance at the Society for Adolescent Health and Medicine national meeting.

2. Travel for CRC to Transgender Health Clinic sessions at CCHMC Satellite locations ($7,426, Years 1-3): The Transgender Health Clinic holds clinics at the main hospital campus, as well as at satellite locations in (b)(6) (b)(6) Clinics are held at (b)(6) (b)(6) Thus, the CRC will be traveling to (b)(6) satellite locations (b)(6) Using the 2021 IRS rate for mileage reimbursement, we request $7,426 for staff travel over the first 2.5 years of the study.

3. Transportation for participants to study visits ($10,800 total, Years 1-5): While youth under the age of 18 years will be required to have parental consent to participate in the study and thus are likely to have access to transportation, youth over the age of 18 years may not. Many transgender youth face financial and transportation barriers, and some may be living with friends or others due to no longer being welcome by their families. We are requesting funds to provide transportation (i.e., bus cards, Uber [for which there is an institutional account]) for an estimated 40 youth, for 6 in-person study visits, at an estimated cost of $45 round trip.

4. Parking at CCHMC is no-cost for patients and families accessing services. Thus, no funds are requested.

D. Other Direct Costs: ($307,096)

1. **Publication costs ($3,000 total, Years 2 and 5)**: We are requesting fees to cover publication costs associated with the minimum of 4-6 manuscript that we expect to originate from this work.

2. **Internal Purchased Services:**

   a. **Schubert Research Clinic ($33,141 over 5 years):** This study will utilize the Schubert Research Clinic at Cincinnati Children's Hospital Medical Center. We have budgeted 2 hours of use of the clinic for each in person study visit (baseline, 3, 6, 12, 18, and 24 months; total of 6 visits). This cost includes use of clinic rooms, nursing time for vital signs, phlebotomy services, and all needed supplies for phlebotomy. The total is for 5 years and is budgeted per year based on the study timeline.
   b. **Laboratory Studies performed through the Clinical Laboratory ($39,442 over 5 years):** We will plan to have the Complete Blood Count, Estradiol, Total Testosterone, and Sex Hormone Binding Globulin run in the CCHMC Clinical Laboratory. See study schedule of events (Table 4) for frequency of laboratory studies. The total is for 5 years and is budgeted per year based on the study timeline.
   c. **Laboratory Studies performed in the Hemostasis-Thrombosis Laboratory ($71,201 over 5 years):** The Hemostasis-Thrombosis Laboratory will perform the von Willebrand antigen and activity, total and free Protein S, and Protein C activity. To minimize cost, these studies will be batched and ran as a cohort of samples are available. See study schedule of events (Table 4) for frequency of laboratory studies. The total is for 5 years and is budgeted per year based on the study timeline.
   d. **Laboratory Studies performed in the (b)(6) Laboratory ($78,859 over 5 years):** The (b)(6) (b)(6) Laboratory will perform the remaining studies (TFPI, Fibrinogen, Factor VIII, D-dimer, Prothrombin 1+2 fragment, thrombin generation assay, thrombophilic polymorphisms, platelet activation studies, activated protein C resistance). To minimize cost, these studies (except for the platelet studies, which will be run in real time) will be batched and ran as a cohort of samples are available. Additionally, the (b)(6) Laboratory will bank plasma, DNA, platelet proteins, and platelet RNA for those that consent for the repository. These costs include kits for these assays as well as general laboratory consumables (i.e., pipette tips, microfuge tubes, conical tubes, buffers, personal protective equipment, etc.). See study schedule of events (Table 4 in approach) for frequency of laboratory studies. The total is for 5 years and is budgeted per year based on the study timeline.
   e. **Study Recruitment Flyers ($195 total, Year 1):** We will utilize CCHMC Office of Clinical and Translational Research marketing services to produce recruitment flyers to be placed in the Transgender Health Clinic for a total cost of $195. This cost includes collaboration with marketing services ($50), services to design the flyer ($85), and printing of recruitment flyers ($60).
   f. **Study Newsletters ($9,795 total, Years 1-5)**: As part of our retention strategy we will utilize CCHMC Office of Clinical and Translational Research marketing services to produce quarterly newsletters (total of 16) for study participants. This cost includes collaboration with marketing services ($192/each =$3,075 total) and services to design newsletters ($420/each = $6,720). Newsletters will be disseminated by the research team.

3. **Participant incentives:**
   a. **Patient Incentives ($50,625 over 5 years):** These are the incentives for participation and retention in the proposed studies. This includes $100/visit for in-person visits, which totals 6 visits per subject. This also includes $25/phone call visit, which are at 9, 15, and 21 months (total of 3 visits). The total is for 5 years and is budgeted per year based on the study timeline.
   b. **Aim 2.1: Interviews with Hematologists ($3,000, Year 1):** We intend to recruit up to 20 participants for this phase but will maintain flexibility in this number in order to ensure that we reach informational redundancy in our data. Thus, we are requesting funds to provide incentives for up to 30 participants. Participants will receive $100 in compensation for their time.

c. **Aim 2.2a: Cognitive Interviews for Developing Survey Items ($1,000 total, Years 2 and 3):** We intend to recruit up to 10 participants for this phase. Participants will receive $100 in compensation for their time.
d. **Aim 2.2b: Pilot Testing for Developing Survey Items ($1,000, Year 3):** We intend to recruit up to 20 participants for this phase. Participants will receive $50 in compensation for their time.
e. **Aim 2.3: Survey of Hematologists ($7,400, Year 4):** We plan to send 370 surveys in order to meet our target number of completed surveys, and we are requesting sufficient funds for a high response rate given that the topic of the survey is timeline and of high interest to potential participants, who will be reached through recruitment via a topically-relevant professional organization. Participants will receive $20 in compensation for their time.

4. **Transcription Services:** Transcription services will be provided by an independent transcription agency.
   a. **Interviews with Hematologists ($3,375, Year 1):** We request funds for 30 interviews lasting an estimated 75 minutes each ($1.50/min).
   b. **Cognitive Interviews for Developing Survey Items ($1,575 total, Years 2 and 3):** We request funds for 10 interviews lasting an estimated 105 minutes each ($1.50/min).
5. **Mailing Costs ($238 total**, Years 1-4): Incentives will be mailed to participants vis U.S. Postal Service (first class, $0.55/each).
6. **Qualitative Data Analysis Software ($1,250, Year 1):** Funds are requested to upgrade the qualitative data analysis software that will be used by the PI and CRC (Nvivo) to the most recent version.
7. **American Medical Association Masterfile Data (AMA) ($2,000, Year 4):** Should we fail to reach our target number of completed surveys, we will obtain a list of physicians who practice adult or pediatric hematology in the U.S. (and their contact information) from a third-party vendor (Redi-Data). This vendor provides access to physician data collected by the American Medical Association (AMA), including contact data for over 1 million physicians. The AMA Masterfile includes all US trainees who entered medical school and includes prospective data from primary sources throughout a physician's career. All medical doctors are included, regardless of AMA membership.

Total Direct Expenses: $1,845,239

Total Indirect Expenses: $1,088,692

Children's Hospital Medical Center's federally negotiated indirect cost rate agreement for on-campus research is 59% of modified total direct costs, which excludes exclude equipment, capital expenditures, charges for patient care, student tuition remission, rental costs of off-site facilities, scholarships, and fellowships as well as the portion of each subgrant and subcontract in excess of $25,000.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		868,920.00
Section B, Other Personnel		642,597.00
Total Number Other Personnel	9	
Total Salary, Wages and Fringe Benefits (A+B)		1,511,517.00
Section C, Equipment		0.00
Section D, Travel		26,626.00
1. Domestic	26,626.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		307,096.00
1. Materials and Supplies	0.00	
2. Publication Costs	3,000.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	232,633.00	
9. Other 2	63,025.00	
10. Other 3	8,438.00	
Section G, Direct Costs (A thru F)		1,845,239.00
Section H, Indirect Costs		1,088,692.00
Section I, Total Direct and Indirect Costs (G + H)		2,933,931.00
Section J, Fee		0.00
Section K, Total Costs and Fee (I + J)		2,933,931.00

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 09/30/2024

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ○ No

If "Yes" to euthanasia

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

○ Yes ○ No

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

2. *Program Income Section

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

○ Yes ● No

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

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

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

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3. Human Embryonic Stem Cells Section

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

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

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

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ○ Yes ● No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ● No

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

*Previously Reported: ○ Yes ○ No

6. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

Funding Opportunity Number: PA-20-185 . Received Date: 2021-11-05T08:26:18.000-04:00

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 09/30/2024

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	Introduction.pdf
Research Plan Section	
2. Specific Aims	Specific_Aims.pdf
3. Research Strategy*	Research_Strategy.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	Letters_of_Support_Combined.pdf
10. Resource Sharing Plan(s)	
11. Authentication of Key Biological and/or Chemical Resources	Authentication_of_Key_Resources.pdf
Appendix	
12. Appendix	Appendix_1_Aim_2_Phase_1_Draft_Interview_Conte.pdf

Tracking Number: GRANT13498164
Funding Opportunity Number: PA-20-185. Received Date: 2021-11-05T08:26:18.000-04:00

INTRODUCTION TO THE REVISED APPLICATION

We appreciate the helpful critiques and many positive comments, such as (b)(4); (b)(6) (b)(4); (b)(6) and (b)(4); (b)(6) (b)(4); (b)(6) (b)(4); (b)(6) We addressed the reviewers' (R) concerns in the revised application; as a result it is much stronger. Changes in the Research Plan are marked with a bar in the margin.

(b)(4); (b)(6)

SPECIFIC AIMS

Many of the 2.7% of US youth[9-11] who identify as transgender or gender nonconforming (hereafter transgender [TG]) experience gender dysphoria, associated with negative health outcomes including depression and suicide.[10,12] Up to 60% of TG youth have attempted suicide.[10,12] One of the most effective and recommended[13,14] interventions to reduce gender dysphoria and suicide risk in TG youth is gender-affirming hormone therapy (GAHT), the use of hormones to promote congruence with affirmed (identified) gender.[15-17] GAHT for TG women includes estrogen and androgen blockade.[13,14] In cisgender women (assigned female at birth, identify as female), estrogen-based hormone replacement therapy and contraception is associated with significantly increased risk of thrombosis,[18-20] with measurable changes in procoagulant factors and inhibitors of coagulation leading to increased thrombin generation.[21-24] Estrogen GAHT in TG women (assigned male at birth, identify as female) is also associated with increased risk of thrombosis.[25,26] *These studies reporting an association of GAHT with thrombosis were conducted with outdated treatment regimens and did not include TG youth, who are likely to receive GAHT for a much longer time than TG adults.* It is also unknown what, if any, changes in the hemostatic system occur with estradiol GAHT. ***In our previous work, a majority of TG youth starting GAHT had preexisting personal/family risk factor(s) for thrombosis***.[6] Although no thromboses occurred in this short-term study, multiple patients received thromboprophylaxis with GAHT start.[6] *With no data-based guidelines to inform management, wide variation exists in how hematologists – even in the same institution – approach treatment decisions about thromboprophylaxis for TG youth who are at increased risk of thrombosis.*[6] No data exist about the attitudes and practices of hematologists around recommending such prophylaxis to youth. *What is unknown* includes: 1) whether estrogen GAHT provided per current guidelines[13,14] leads to increased risk of thrombosis by inducing prothrombotic changes in TG women (who also have testosterone present); and 2) the factors influencing the recommendations of clinicians about thromboprophylaxis for TG youth with other risk factors for thrombosis. These data are vital for clinicians to provide accurate information to patients and families about the risks of GAHT and to advise them in making informed decisions about GAHT and potentially thromboprophylaxis.

Our *long-term goal* is to improve the physical and mental health of TG youth through understanding the thrombotic risks associated with estrogen GAHT and developing mitigation strategies. ***The objectives of this proposal are to prospectively examine prothrombotic changes in coagulation factors in a cohort of TG youth receiving estrogen GAHT and to examine the attitudes and practices of hematologists about thromboprophylaxis for youth on GAHT***. The *rationale* underlying this objective is that adult studies suggest that thrombosis risk increases with longer time on GAHT,[25,26] but no study has systematically evaluated whether prothrombotic changes develop with GAHT. *Determining if estradiol GAHT induces prothrombotic changes is a key first step in understanding its thrombotic risk.* We found that many TG youth had preexisting thrombosis risk factors,[6] which may compound this risk. With no guidance on how to safely manage youth at higher risk of thrombosis who start GAHT, clinicians are making recommendations with the limited available data. In similar situations, our team found that lack of clinical guidance was associated with significant practice variation.[27,28] Our team has expertise in hemostasis[29,30] and defining factors impacting clinician management decisions.[28,31,32]

We plan to achieve our objectives through the following specific aims:

Specific Aim 1: In a population of TG women (up to age 22 years at GAHT start), prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen GAHT. *Hypothesis: Youth receiving estrogen for GAHT will exhibit progressive prothrombotic changes in the coagulation system that increase with longer time on GAHT.* Hemostatic parameters (such as D-dimer, activated protein C resistance, clotting factors, etc.) will be assessed at 0, 3, 6, 12, 18, and 24 months. TG youth will also be assessed for adherence to GAHT, changes in personal/family risk factors, and thrombotic events.

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to TG youth with personal/family risk factors that increase thrombosis risk. *Hypothesis: Greater perceived benefits of GAHT will be associated with intention to recommend thromboprophylaxis to TG youth at risk for thrombosis.* Both practices and intentions will be assessed as some hematologists may not yet have cared for TG youth. Decision-making about prophylaxis will be explored (i.e., weighing risks and benefits). First, regional pediatric and adult hematologists will be interviewed. Then this data will be used to develop a new survey designed to understand the influential factors in decisions about prophylaxis that will be disseminated to U.S. and Canadian hematologists during the final part of this aim.

Through the novel focus on youth, comprehensive examination of hemostatic parameters, and inclusion of clinicians, *this work will generate new understanding* of prothrombotic changes during estrogen GAHT and of clinician decision-making about thromboprophylaxis for youth starting GAHT who have other risk factors for thrombosis. The next steps in this line of research are to use the data generated to develop educational interventions and clinical guidance for gender care clinicians and hematologists to optimize care for TG youth starting GAHT.

RESEARCH STRATEGY

I. Significance

Gender-affirming hormone therapy (GAHT) decreases suicide risk among transgender and gender nonconforming (hereafter TG) people. Among the 1.6 million TG Americans,[1] gender dysphoria is associated with significantly increased risk of suicide. TG persons report a *9-fold increased rate of suicide attempts* compared to cisgender people.[12] TG adolescents also report increased suicidal ideation.[11] GAHT is associated with amelioration of gender dysphoria and reduced suicide risk.[15,16,33] However, estrogen GAHT may be associated with an increased risk of thrombosis, both arterial and venous.[25,26] For clinicians to fully assess the risk-benefit ratio associated with GAHT, better characterization of thrombosis risk is needed. Previous studies examined thrombosis risk among participants using GAHT formulations that are no longer recommended.[13,14] Further, studies have not included adolescents under age 18 years. Thus, there is a critical gap in knowledge about thrombosis risk in adolescents, which is significant because *adolescent TG women will likely have substantially longer exposure to GAHT than TG adults and thus may be at the greatest risk for thrombotic complications*.

Estrogen in cisgender women is associated with prothrombotic changes in hemostatic factors. Estrogen induces prothrombotic changes in coagulation factors in cisgender women using hormonal contraception[21,22] and hormone replacement therapy.[23,24] (**Table 1**) Estrogen increases procoagulant factors that contribute to increased thrombin generation and thrombotic risk,[21-24] most notably prothrombin (factor II), factor VIII, fibrinogen, and von Willebrand factor (VWF).[21,34-39] Simultaneously, estrogen diminishes inhibitory proteins, such as tissue factor pathway inhibitor (TFPI), total protein S, free protein S, and antithrombin III (ATIII).[40-46] Estrogen also induces activated protein C (APC) resistance (APCr).[21,24,47-49] The limitation to these studies is that all were conducted in cisgender women using either estrogen-containing contraception or hormone replacement therapy. Little is known about the impact of estrogen for GAHT, managed per current guidelines, on coagulation factor expression and changes in thrombin generation. Limited data exists on the impact of estradiol GAHT on hemostatic factors in adult TG women on stable hormone doses. One study found that both maximal amplitude of thromboelastography (TEG) and the area under the curve (AUC) of thrombin generation assays (TGA) were elevated in TG women on estradiol.[50] Although transdermal estradiol is thought to have less risk of thrombosis due to lack of first-pass effect, both oral and transdermal estradiol GAHT had similar effects on both the TEG and TGA.[50] A second study found elevations in factors II, IX, and XI.[46] Neither study comprehensively examined changes in thrombotic risk over time.[46,50] Although less well defined, estrogen also may have a prothrombotic effect on platelets. Data suggest that platelets from women have increased activation potential versus platelets from men.[51] Murine data support this finding.[52-54] *To date, no study has comprehensively examined the impact of estradiol GAHT on thrombotic factors or platelet activation in TG women*.

Table 1. Estrogen Effects on Coagulation

Procoagulant factors	Effect	Inhibitor of Coagulation	Effect
Prothrombin	↑	Tissue Factor Pathway Inhibitor	↓
Factors VIII, IX, XI	↑	Total Protein S	↓
Fibrinogen	↑	Free Protein S	↓
von Willebrand Factor	↑	Activated Protein C	Induced Resistance

The thrombosis risk of using estrogen GAHT in youth as per current practice guidelines is unknown. The risk of thrombosis associated with estrogen-containing contraceptives or hormone replacement therapy is well documented.[18-20] Estrogen GAHT was associated with increased risk of venous thromboembolism, stroke, and myocardial infarction,[25,26] but these studies included exclusively adult TG women using ethinyl estradiol for GAHT - which is no longer the recommended formulation. *Thus, all studies suggesting an increased risk of thrombosis with estrogen GAHT were conducted prior to current practice guidelines.* The current guidelines recommend titrating hormone doses based on serial estradiol levels to maintain levels within physiologic range.[13,14] Further, estradiol currently is recommended for GAHT and may be of decreased thrombosis risk. The only study to date that evaluated thrombosis risk with GAHT among only adolescents and young adults was generated by our research team.[6] We found that estradiol GAHT used per current guidelines was not associated with incident thrombosis, at least in the short-term (median follow-up: 1.4 years).[6] However, our study had limitations. First, most studies of estrogen GAHT show increased thrombosis risk with longer duration of therapy.[25,26] Therefore, longer-term studies are needed among youth. Further, data suggest that, regardless of whether ethinyl estradiol or estradiol is used for GAHT, estrogen does impact coagulation parameters.[25,26,46,50] *A prospective study of TG youth treated in accordance with current clinical guidelines is needed to evaluate thrombosis risk and procoagulant changes in order to inform decision-making about GAHT and thromboprophylaxis. This is a critical first step to determine if larger, multicenter studies are warranted to assess thrombotic incidence in TG individuals initiating estrogen GAHT.* Unlike our published work that only evaluated incidence of thrombosis,[6] this study seeks to determine the degree of prothrombotic change (if any) resulting from GAHT. This first-step will provide rationale for a future study and determine effect magnitude, allowing estimation of sample size for that future study.

Transgender women on GAHT do not necessarily have the same thrombosis risk compared to cisgender women. Unlike cisgender women who primarily have unopposed estrogen, TG women continue to produce testosterone. The combined thrombosis risk of estradiol in the setting of continued production of testosterone has not been defined. Estradiol does suppress testosterone levels.[13] The recommended target for testosterone for TG women is the normal level for premenopausal cisgender women.[14] However, to achieve desired results from GAHT, higher doses of estradiol (vs. hormone replacement therapy in cisgender women) may be needed to both promote female secondary sexual characteristics and suppress endogenous testosterone.[13,55] The impact of this unique hormonal milieu on many physiologic processes, including hemostasis, is unknown. In our cohort, median testosterone level for TG women was 189.5 ng/dL (interquartile range 15.2-367)[6] compared to the range of 0.1-29 ng/dL in a study of cisgender women.[56] While the impact of estrogen in physiologic states (i.e., puberty, pregnancy, menopause)[49,57-62] or during treatment (i.e., oral contraceptives or hormone replacement)[21-24] among cisgender women is known, no studies provide a comprehensive evaluation of hemostatic changes with initiation of estrogen GAHT in transgender women. *An understanding of the unique thrombotic risks associated with use of estrogen for GAHT in the setting of endogenous testosterone is critical for physicians treating TG youth to counsel about risks associated with GAHT.*

Given the lack of clear data about thrombotic risk and absence of clinical guidelines, clinicians are likely to exhibit variability in practice that may adversely impact patient outcomes. In the only study to date of thrombosis risk among TG youth on GAHT, our team found inconsistent referral patterns among TG clinicians for hematologic evaluation for youth with personal or family risk factors for thrombosis (unpublished data,[6]) and differences among pediatric hematologists with respect to recommending thromboprophylaxis, continuing prophylaxis for youth with history of thrombosis prior to GAHT, and prescribed prophylactic agent.[6] Further, despite a lack of consistent data to support an increased risk of thrombosis for youth using testosterone GAHT, prophylaxis was recommended to two such youth with personal or family history of thrombosis.[6] Our team has described similar variations in practice among clinicians considering other biomedical prevention measures for youth.[27,28,31,32] *Because patient outcomes can be negatively impacted by variations in practice, understanding the factors contributing to such variability provides critical information to develop clinical guidance for hematologists to standardize care while maximizing benefit and minimizing mortality.*

Information about which patients would benefit from further evaluation and thromboprophylaxis is urgently needed to foster informed recommendations by clinicians as well as decision-making by patients and families as they weigh risks and benefits of GAHT and thromboprophylaxis. In order to ethically support transitioning youth, physicians must weigh the risks and benefits of GAHT for each patient while also "communicating the risks of physical iatrogenic effects of hormone therapy."[63] Although the risks of failure to treat gender dysphoria are well documented,[64,65] the risk of thrombosis related to GAHT in youth remains unclear,[64] and guidance about which patients should be considered at higher risk of thrombosis and warrant referral for further hematologic evaluation is lacking. Further, no medications are FDA-approved for the indication of thromboprophylaxis for pediatric patients in the outpatient setting, and thromboprophylaxis itself is not without risk. *In order to provide patients and families with the information necessary for informed consent about GAHT, an understanding of which patients are at higher risk of thrombosis and thus should undergo hematologic evaluation and which patients might benefit from thromboprophylaxis is urgently needed.*

Crucial limitations in the literature provide the ***scientific premise*** underlying this proposal. Published studies included participants using GAHT products that are no longer recommended in current guidelines, and guidelines recommend titrating hormone doses based on serial estradiol levels to maintain physiologic levels,[13,14] which may also impact thrombosis risk. Prior studies did not include adolescents under age 18 years, which is significant because adolescent TG women will likely have longer exposure to GAHT than adults and thus may be at greater risk for eventual thrombosis. Although studies demonstrate increased thrombosis risk in older TG women, *no studies have comprehensively examined prothrombotic changes in hemostatic factors in young TG women on GAHT nor in the setting of the unique hormonal milieu of TG women with both exogenous estrogen and endogenous testosterone. In addition, the lack of data about the thrombosis risk in TG youth on GAHT negatively impacts clinical care.* Clinicians lack the data necessary to counsel patients and families about risks of GAHT and to understand themselves which patients need further evaluation prior to GAHT start. *The proposed work extends the findings of past studies by providing critical data necessary for clinicians, patients, and parents to assess the thrombosis risk of GAHT while also providing key information about clinician attitudes, practices, and intentions toward prescribing thromboprophylaxis to TG youth at increased risk of thrombosis, and factors associated with these intentions.* Our findings will have direct impact on the clinical care of TG youth by providing an understanding of thrombotic risk of GAHT for youth, as well as informing development of future clinical guidance targeting hematologists and clinicians providing gender care to optimize and standardize clinical care.

II. Innovation

Gender-affirming hormone therapy (GAHT) is recommended by the World Professional Association for Transgender Health[13] and the Endocrine Society[14] as part of optimizing care of TG people. Although studies are examining other potential adverse effects of GAHT in TG youth,[66-70] there are no existing data about the thrombotic risks associated with GAHT among youth to guide patients, families, and clinicians. *The proposed research fills this critical gap by developing new knowledge needed to advance the field and thus is* ***innovative in 5 ways****: 1) it is the first to focus exclusively on TG youth, who are likely to receive GAHT for a longer period of time than TG adults; 2) it is the first to specifically examine changes in biomarkers of thrombosis in youth receiving estrogen GAHT; 3) it is the first to comprehensively explore changes in hemostatic factors in the setting of exogenous estrogen and endogenous testosterone; 4) it will provide insight from hematologists about which TG youth would be considered at higher risk of thrombosis; and 5) it explores the factors influencing the recommendations of hematologists for thromboprophylaxis among TG youth with personal/family risk factors for thrombosis.* Thus, this study will generate the information about thrombosis risk that clinicians need in order to counsel patients and that patients and families need to make decisions about GAHT and thromboprophylaxis. It also will provide key information about which youth should be considered for further evaluation and potentially thromboprophylaxis. ***This knowledge is critical to the development of clinical guidance and tools for both gender care clinicians and hematologists in order to standardize clinical practice, reduce inequities in care, and improve patient outcomes.***

III. Approach

III.A. Relevant Research by Investigators

Tanya Mullins, MD, MS is an adolescent medicine physician-scientist at Cincinnati Children's Hospital (CCHMC) focused on optimizing the health of adolescents and young adults. Her work demonstrates that various factors impact clinician intentions to prescribe medication for prevention of HIV,[28,31,32] and variability in practice is likely to occur in the absence of clinical guidelines.[27] Dr. Mullins has expertise leading and conducting research (funded by the NIH-funded Adolescent Medicine Trials Network for HIV/AIDS Interventions and NICHD K23) utilizing methodology that is relevant to all phases of the proposed research, including studies recruiting youth[71,72] and physicians,[27,28,31,32] qualitative research methods,[27,28,31] and survey research methods.[32,73]

(b)(6) **MD** is a pediatric hematologist at CCHMC whose career focuses on better understanding of the coagulation system. His laboratory has focused on understanding the roles of coagulation factors in driving immune function.[29,74-78] He has significant experience with laboratory coagulation studies, and his laboratory has experience running the proposed laboratory studies. (b)(6) has experience with clinical trials in hemophilia. He served as the local principal investigator on several multi-center trials, leading to multiple publications.[30,79-82]

(b)(6) **DO** is an adolescent medicine physician, and (b)(6) the CCHMC Transgender Health Clinic, which has cared for nearly 2000 youth since its inception in 2013. Together, **Drs.** (b)(6) **and** (b)(6) collaborated on a retrospective review of all TG patients receiving GAHT in the Transgender Health Clinic to examine risk factors for and occurrence of thrombosis. *This is the only study of thrombosis risk in exclusively TG youth to date.[6] Thus, this team is uniquely positioned to conduct this study*.

(b)(6) **MD** is an adolescent medicine physician-scientist at CCHMC who served for 17 years as the local principal investigator for the Breast Cancer and the Environment Research Program, following a longitudinal cohort of girls recruited at ages 6-7.[83-90] He adds complementary expertise in sex hormone physiology and recruitment and retention of a longitudinal cohort.

(b)(6) **PhD** (CCHMC, Experimental Hematology) has expertise in platelet biology and differential activation.[91-93] (b)(6) **PhD** (CCHMC, Biostatistics/Epidemiology) provides statistical expertise.[94-96]

III.B. Specific Aim 1: In a population of TG women (up to age 22 years at GAHT start), prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen GAHT. Primary hypothesis: *Youth receiving estradiol for GAHT will exhibit progressive prothrombotic changes in the coagulation system that increase with longer time on GAHT.* **Sub-Hypotheses: 1)** Other risk factors for thrombosis (obesity, tobacco use, etc.) will be associated with increased prothrombotic changes in the hemostatic system of TG women; **2)** Estradiol and testosterone levels will be correlated with prothrombotic changes in coagulation parameters; **3)** Estradiol contributes to increased activation of platelets in TG women.

III.B.1. Scientific Rationale: Preliminary Data and Relevant Literature

Use of exogenous estrogen has procoagulant effects on hemostatic factors, but studies of estrogen for GAHT have critical limitations. The effects of estrogen on hemostatic factors, as described above, include increased levels of prothrombotic factors with simultaneously diminished inhibitors of coagulation. Increased factor VIII, decreased total and free protein S, and increased acquired APCr may lead to thrombosis.[34,38] This combination of effects leads to a significant increase in thrombosis risk, based on prior studies of hormonal

contraceptives, replacement, and GAHT.[18-20,25,26] However, most studies that demonstrated an increased risk of thrombosis with GAHT have limitations that prohibit application to current practice. These limitations are inclusion of patients on ethinyl estradiol and lack of monitoring of estradiol levels, both of which may significantly impact the risk of thrombosis.[25,26] *Thus, critical data about the effect of estrogen GAHT on hemostatic factors is missing.*

Over half of TG youth have a historical risk factor for thrombosis,[6] and laboratory testing for underlying biological risk factors that might amplify this risk is not standard of care. Currently the only data on risk of thrombosis in young TG women treated per current guidelines were generated by our group.[6] Among our cohort of 611 TG adolescents and young adults who started GAHT, 52% had personal risk factors (35% had obesity [body mass index (BMI)>30], 15% used tobacco, nearly 5% had migraine with aura) or family risk factors for thrombosis (8% with family history of thrombosis, 0.8% with family history of thrombosis risk factors). Obesity is an independent risk for thrombosis and increases APCr.[97,98] In cisgender women, obesity combined with estrogen further increases thrombosis risk over that for women with normal BMI.[99] Although relatively few youth were tested for underlying thrombophilia, 70% of those tested had at least one abnormal result associated with increased risk of thrombosis.[6] Further, 3 youth had personal history of thrombosis prior to starting GAHT. Although we did not observe any thromboses in our cohort, median follow-up time was only 1.4 years.[6] Other studies suggest that thrombosis risk increases with duration of GAHT.[25,26] *Our preliminary data suggest that many youth starting GAHT may be at increased risk of thrombosis prior to starting estradiol.* **Many of these underlying prothrombotic risk factors (Table 2[100-108]) are synergistic with estrogen, with a 20-30-fold increase in thrombosis risk in combination with estrogen.[109,110]** *Understanding the thrombotic risks of estradiol GAHT is critical for informed consent and optimizing recommendations about anticoagulation for youth with pre-existing risk factors and potential prothrombotic risk from GAHT.*

Table 2. Common Risk Factors for Thrombosis

Risk Factor	Risk (Fold Increase)
Heterozygosity for Factor V Leiden	7
Elevated Factor VIII (>175%)	5-10
Prothrombin G20210A Polymorphism	4
Thrombosis in First Degree Relative	2-4
Obesity	2.9-4
Cigarette Use	1.9-2.8

There is a paucity of data on the effect of GAHT on hemostatic factors. To date, two studies have examined the effect of GAHT on hemostatic parameters in TG women.[46,50] In both studies, the participants were all adults using estradiol. The first study found that GAHT increased both peak and total thrombin production vs. cisgender controls. TG women also exhibited increased thrombus strength.[50] In the second study, elevations in factors IX and XI and fibrinogen were associated with GAHT.[46] Further, decreased levels of protein C also correlated with estrogen GAHT.[46] Neither study assessed hormone levels, and neither were prospective.[46,50] GAHT also is associated with increased platelet production, which increases with each year of GAHT.[111] However, no studies have yet examined the impact of estrogen GAHT on platelet activation. *Given that TG youth are likely to be taking GAHT for a longer time than TG adults, a detailed and complete understanding of procoagulant changes in hemostatic factors is critical to allow providers to accurately counsel patients and families about GAHT risks.*

Based on this rationale, we hypothesize that **estrogen GAHT as currently recommended is associated with acquired changes of the hemostatic system that predispose to an increased risk of thrombosis and that prolonged use of estradiol GAHT is associated with progressive rise in risk**. Evaluation of the procoagulant changes associated with GAHT may also allow determination of the most important markers for those who may be at greatest risk for thrombosis.

Table 3. Inclusion and Exclusion Criteria

Inclusion Criteria
- Diagnosed with gender dysphoria
- Clinical care at the CCHMC Transgender Health Clinic
- Initiation of estradiol GAHT
- Age ≤ 22 years at start of GAHT
- Able to understand written and spoken English

Exclusion Criteria
- Personal history of thrombosis
- Personal history of bleeding disorder
- Personal use of anticoagulation during GAHT (except standard of care use around surgery)
- Inability to comply with study procedures or

III.B.2. Subjects and Recruitment

III.B.2.a Transgender Health Clinic (THC)*:* Participants will be recruited from the multidisciplinary THC in the Division of Adolescent and Transition Medicine at CCHMC. Since 2013, the THC provides TG care to youth from a four-state catchment area (Ohio, Kentucky, Indiana, West Virginia). The THC is one of the largest pediatric TG clinics in the U.S. Between July 2013 and March 2019, the clinic cared for 1406 individuals, and GAHT was initiated in 611 patients, including 182 TG women. Demand for care in this clinic has been high since its inception, and we expect this trend to continue given national increases in youth seeking TG care.[112] In each of the last 3 years, approximately 300 new patients were seen in the clinic.

III.B.2.b. Subjects: Seventy-five youth 22 years old or younger will be recruited prior to starting estradiol GAHT and followed for 24 months. Full inclusion/exclusion criteria are in **Table 3**. TG patients are seen every 6 months in the THC. See **Table 4** for schedule of study visits. In 2019, 62 patients

Table 4. Study Schedule of Events

Timeline (months)	0	3	6	9*	12	15*	18	21*	24
Informed consent	x								
Confirm GAHT dose; Assess Adherence	x	x	x	x	x	x	x	x	x
Concurrent medications	x	x	x	x	x	x	x	x	x
Assessment of other risk factors**	x	x	x	x	x	x	x	x	x
Determination of thrombosis	x	x	x	x	x	x	x	x	x
Labs***	x	x	x		x		x		x

*Visits at 9, 15, and 21 months to be conducted via phone call. **For other risk factors, see text of grant. ***For lab schedule, please see Table 5.

aged 22 or younger started estradiol GAHT; 67% of patients in the target age were retained from 2019 to 2020.

III.B.2.c. Sex as a biologic variable: Only TG women will be enrolled: the impact of currently recommended estradiol GAHT on hemostatic factors is unknown, but prior studies suggest that estradiol GAHT increases thrombosis risk. Testosterone GAHT for TG men is not a significant risk factor for thrombosis.[25]

III.B.2.d. Recruitment and retention: Participants will be recruited directly from the THC by a research coordinator who will conduct study visits and follow-up phone calls. Participants will receive $100 for each completed in-person visit and $25 for each completed phone visit. To maximize retention, study visits will be scheduled in coordination with THC visits when possible. Further retention strategies effective in other studies will be used (i.e., study newsletter, updated contact information), as detailed in Aim 1 Recruitment and Retention Plan.

III.B.3. Data Collection: Coagulation testing will be done at baseline, 3 and 6 months after starting estradiol, and every 6 months thereafter for the first 2 years of GAHT (see **Table 5**). Each participant serves as her own control given the unique hormonal milieu of TG women as described above.

Table 5. Lab Schedule

Visit (Months)	0	3	6	12	18	24
Labs:						
CBC	X		X	X	X	X
Estradiol and testosterone	X	X	X	X	X	X
Factors II, VIII, IX, XI	X	X	X	X	X	X
von Willebrand Factor (antigen and activity)	X		X	X		X
Fibrinogen	X	X	X	X	X	X
Protein C	X	X	X	X	X	X
Total and Free protein S	X	X	X	X	X	X
Activated protein C resistance	X	X	X	X	X	X
Tissue factor pathway inhibitor	X		X	X		X
Thrombin generation assay	X	X	X	X	X	X
Plasminogen activator inhibitor – 1 (PAI-1)	X		X	X		X
D-dimer, Prothrombin 1.2 fragment	X		X	X		X
Assessment of platelet hyperactivity	X			X		X
Thrombophilic polymorphisms	X					
Banked DNA	X					
Banked Plasma	X	X	X	X	X	X

Assessment of thrombosis and thrombosis risks: Although the primary outcome is not thrombosis due to the expected low frequency of events, we will ask each participant about interim occurrence of thrombosis (arterial or venous) at every 3-month study interaction. Based on our preliminary data showing that many TG youth have other risk factors for thrombosis,[6] participants will be assessed for new-onset thrombosis risks, including tobacco use, BMI (in-person visits), and new personal medical diagnoses that may increase risk for thrombosis (i.e., inflammatory bowel disease, migraine with aura, etc.). Assessment of new family history of thrombosis or thrombosis risk factors will also be done. Evaluation of risk factors at each visit is necessary to capture potential confounding factors for thrombosis events and changes in the coagulation system.

Hormone usage: Adherence to GAHT may vary over time; participants will be evaluated every 3 months for type and dose of GAHT prescribed and taken. Consistent with best practice guidelines,[113] adherence will be assessed via multi-method approach by self-report (visual analog scale of adherence,[114,115] last missed dose, number of missed/late doses in the past week[116,117]) and using objective data from estradiol and testosterone levels. We will assess for correlation between the subjective and objective measurements of adherence. At the study visits indicated in **Table 5,** blood will be obtained to measure estradiol and testosterone levels. Data from hormone replacement therapy in Turner Syndrome suggest limited variability of estradiol levels over the course of a day, even with oral dosing.[118] Therefore, testing will be conducted whenever study visits occur (time from last dose will be noted). Sex hormone binding globulin testing will be conducted at the CCHMC clinical laboratory via immunofluorescent assay. Estradiol and testosterone, to be performed at ARUP, are assayed via quantitative high-performance liquid chromatography-tandem mass spectrometry, currently the recommended methodology.[119] Free testosterone and free estradiol will be calculated using concentrations of sex hormone binding globulin and total testosterone and estradiol, respectively.[120] A fixed value will be used for albumin, as published.[121,122]

Assessment of coagulation parameters: The primary outcome is changes in the coagulation system that follow initiation of estradiol GAHT. *We will obtain a thorough and systematic evaluation of changes in coagulation potential at each study visit* (see **Table 5**). A complete blood count (CBC) will be obtained to evaluate changes in hemoglobin and platelet count. Plasma will be obtained at each in-person visit to measure for evidence of prothrombotic changes in hemostatic factors. The hemostatic factors assayed will be factors II (prothrombin), VIII, IX, and XI; VWF (both VWF:Antigen and VWF:Ristocetin Cofactor Activity); fibrinogen; proteins C and S; free protein S, APCr, and TFPI. Thrombin generation assays (TGA) will also be performed to assess for increased coagulation potential. D-dimer and the prothrombin activation fragment 1.2 will be measured as markers of hemostatic activation. Plasma will be aliquoted and frozen until ready to be analyzed.

Coagulation assays: Assays of coagulation will be overseen by (b)(6) The coagulation assays will be performed in the Division of Hematology Hemostasis Thrombosis Laboratory (HTL) and (b)(6)'s laboratory. The HTL analyzes the clinical specimens for CCHMC for proteins C and S, free protein S, and VWF and thus will be used for these study labs. Protein C activity is determined via clottable activity. Total and free protein S levels as well as VWF antigen levels are determined via immune-turbidimetric assays. VWF activity is assessed via ristocetin cofactor activity. (b)(6)'s laboratory will conduct the remainder of the assays. TFPI (Abcam), fibrinogen (Abcam), D-dimer (Abcam), PAI-1 (Biomatik), and prothrombin 1.2 fragment (Biomatik) will be determined via ELISA. Factors II, VIII, IX, and XI levels will be assayed via chromogenic activity (Rossix).

TGA will be assessed on platelet-poor plasma on a Thrombinoscope (Stago). APCr will be performed as a ratio of the endogenous thrombin potential in TGA in the absence or presence of APC.[123]

Assessment of thrombophilic polymorphisms: To better assess baseline thrombotic risk of participants, thrombophilic polymorphisms will be determined. These assays will be performed in (b)(6) s lab. Genomic DNA will be extracted from whole blood and then used for assessment of both factor V Leiden and prothrombin G20210A carriage (Taqman). The remaining DNA will be banked (see below).

Assessment of estradiol GAHT on platelet activation: Cisgender women have greater platelet reactivity to multiple agonists at baseline, including thrombin (via protease activated receptor-1 [PAR-1]), thromboxane, and ADP, compared to cisgender men.[51] We hypothesize that as TG women start GAHT, their platelet reactivity would gradually increase to be similar to cisgender women. We will utilize a methodology that has been established within the laboratory of our collaborator (b)(6) As previously described, we will evaluate platelet activation on whole blood using flow cytometric analyses prior to GAHT start and 1 and 2 years later.[51] We will assess activation in response to TRAP-1 (PAR-1 agonist), ADP ($P2Y_{12}$ agonist), and U46619 (thromboxane receptor). Platelet activation will be assessed via PAC-1 (activated form of $\alpha_{IIb}\beta_3$) and CD62p (P-selectin) expression via flow cytometry. Activation will be assessed across a spectrum of agonist concentrations.

DNA and Plasma Bank: This prospective study with 2 year follow-up is an opportunity to facilitate future research. Genomic DNA will be isolated to conduct thrombophilic polymorphism assays, after which the remaining DNA will be banked in (b)(6) s laboratory as a repository for future studies. Additional plasma will be obtained, aliquoted, and stored from each study visit (as outlined in **Table 5**). We plan to isolate total protein and RNA from washed platelets[124] and bank this material as well. Samples will be made available upon request to qualified investigators with an approved IRB protocol.

III.B.4. Analytic Plan and Sample Size

Analysis: Our primary outcome is changes in the hemostatic system over the first 2 years of estradiol use for GAHT. **Sub-Analyses:** 1) examine the interactive effects of other personal and family risk factors for thrombosis (i.e., obesity, thrombophilic polymorphisms) with estradiol on changes in the coagulation system; 2) determine the impact of estradiol GAHT on platelet activation; and 3) evaluate the correlation between estradiol and testosterone levels, adherence, and degree of prothrombotic change in hemostatic factors.

Statistical analysis: Descriptive analyses will be used to examine participant characteristics. The difference in continuous variables between baseline and 2-year follow-up will be detected using paired t-test or Wilcoxon signed rank test as appropriate. Linear and nonlinear mixed models will be used to examine trends of change in hemostatic factors/platelet activation over time adjusted for personal/family thrombosis risk factors considering the correlation of repeated measurements in each subject. Univariate and multivariable linear regression models will be used to assess the relationship between personal/family thrombosis risk factors, adherence (self-reported; hormone levels), and changes in hemostatic factors/platelet activation between baseline and 2-years. SAS (v9.4) will be used for analyses. P-values <0.05 will be considered statistically significant.

Sample size calculation was based on linear regression modeling to detect interactive effects of other personal and family thrombosis risk factors (e.g., obesity, tobacco use, thrombophilic polymorphisms) with estradiol on changes in the coagulation system, (e.g., assess the relationship between change in the hemostatic system and obesity). A sample size of 60 achieves 87% power to detect an R-squared of 0.1 attributed to one risk factor (e.g., obesity) adjusted for other risk factors with an R-squared of 0.3 using an F-test with significance level of 0.05. The same sample size also achieves 93% power to detect a difference of 1.8 in mean APCr between baseline and 2-year follow-up (2.2 vs 4.0, respectively) with an estimated standard deviation of difference of 4 and a significance level of 0.05 using a two-sided paired t-test. Seventy-five TG women will be recruited to allow a conservative 20% attrition rate based on retention activities, monetary incentives, and prior studies.[7,8]

III.B.5. Expected Outcomes: *We anticipate that estradiol GAHT will be associated with prothrombotic changes in the coagulation system that will place individuals at greater risk of thrombosis than the general population, and that these changes will progressively increase over time.* We expect an increase in procoagulant factors (factor VIII, fibrinogen, VWF) and concurrent reduction in inhibition of coagulation (decreased TFPI, free protein S; increased APCr). We expect that the increased procoagulant factors and decreased inhibitors of coagulation will additively contribute to a significant increase in thrombin generation and total coagulation potential. We also anticipate that increased platelet activation in the setting of estradiol GAHT will further contribute to the prothrombotic effects of estradiol. Thus, all of these prothrombotic changes will significantly increase the risk of thrombosis for young TG women. *These data will provide the missing information that clinicians need to accurately counsel patients and families about risks of estradiol GAHT, a necessary component of informed consent for treatment.*

III.B.6. Potential Problems and Alternative Strategies

a) Insufficient recruitment and/or retention: We do not anticipate difficulty recruiting because numbers of

new patients in the THC have been stable over the last 3 years, including in 2020 despite the COVID-19 pandemic. Follow-up visits will be scheduled to coincide with THC visits to maximize retention. We will communicate each week with the THC team to assess for new eligible patients. Enrollment will be monitored every 4 weeks.

b) Inability to conduct in-person visits due to COVID-19: If we are unable to conduct in-person visits, study visits will be virtual with subjects coming to the center only for phlebotomy and vital sign measurement.

c) Alternative findings to those hypothesized: Although we hypothesize that estradiol will lead to prothrombotic changes, minimal to no change in the coagulation system may occur. It is also possible that an initial increase in prothrombotic effect may be followed by either a plateau or return to baseline. If either of these scenarios occurred, it would be of *increased* interest, as this outcome would serve to allay the concerns of physicians prescribing GAHT. Based on our design, we will be able to determine any of these potential outcomes.

d) Detection of prothrombotic changes: If prothrombotic changes are found as hypothesized, the current cohort will form the basis of an ongoing cohort to assess ongoing thrombotic risk, supported by future funding.

III.B.7. Scientific Rigor: Scientific rigor is demonstrated through the comprehensive evaluation of the hemostatic system, inclusion of other key personal and family risk factors for thrombosis, use of well-established laboratory tests and experienced personnel in both the HTL and (b)(6) 's laboratory, rigorous power calculation and statistical analysis plan, and experienced team members with complementary expertise.

III.C. Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to TG youth with personal and/or family risk factors that increase thrombosis risk. This aim will be achieved through 3 sequential phases. The first phase will use qualitative methods, which are well suited to developing an in-depth understanding of a previously undescribed phenomena.[125] The data generated in the first phase, along with information learned about personal/family risk factors and prothrombotic changes from the Aim 1 study, will be used to develop a survey in the second phase which will then be administered in the third phase to a national sample of pediatric and adult hematologists who care for youth, producing generalizable data about the attitudes and practices of hematologists toward care of TG youth at increased risk of thrombosis and factors associated with these intentions.

III.C.1. Scientific Rationale: Preliminary Data and Relevant Literature

In the absence of relevant clinical guidelines, clinicians are likely to exhibit variability in practice. Our team's prior work demonstrates that in the absence of formal clinical practice guidelines, clinicians adapt their practices based on their own clinical experience and the perceived needs of their patients.[27] We also found variability in intention to prescribe HIV pre-exposure prophylaxis to adult vs. adolescent patients and by patient risk factors.[32] *Because variability in practice directly impacts clinical care, understanding factors contributing to such variability provides critical information for developing future clinical guidance, such as for clinicians to assist in determining which TG youth should be referred for hematologic evaluation prior to starting GAHT.*

Variability in hematologic management of TG youth at risk of thrombosis exists, likely due to limitations of available data on thrombosis risk. In our review of over 600 TG youth,[6] our team found differences in referral patterns for hematologic evaluation of TG youth prior to starting GAHT. Among 9 youth starting estrogen who had parental history of thrombosis, only 5 were referred for hematologic evaluation prior to GAHT start ([6], unpublished data). There were also differences in management of youth at increased risk of thrombosis among hematologists with respect to whether to initiate thromboprophylaxis, whether to continue prophylaxis among youth with a history of thrombosis prior to GAHT, and what medication was prescribed.[6] Variability in clinical practice exists in other areas of health care of TG youth, such as fertility preservation[126] and use of puberty blockers in non-binary youth.[127] Even when clinical guidelines exist, variation in clinical practice is found, including among pediatric hematologists considering whether to initiate thromboprophylaxis for critically ill pediatric patients with known risk factors for thrombosis.[128] Thus, individual variation between clinicians with respect to evaluation and recommendation of thromboprophylaxis would be expected given the lack of formal guidance. *Understanding the factors influencing the practices of hematologists regarding hematologic evaluation and thromboprophylaxis is the first step in developing clinical guidelines for hematologists to standardize care and guidelines for other TG clinicians for which youth should be referred for further hematologic evaluation.*

Despite lack of data showing an association between testosterone GAHT and thrombosis, thromboprophylaxis is being prescribed to TG men. Studies of cisgender adult men receiving testosterone for treatment of hypogonadism report conflicting results about thrombosis risk, reporting both increased risk and no increased risk of thrombosis.[129-131] However, in studies of GAHT in adult TG men (assigned female at birth who identify as male), testosterone appears to have minimal risk for both venous thromboembolism and stroke.[25,26,132] Yet, in our cohort of TG youth, thromboprophylaxis was recommended to two TG men who had personal or family history of thrombosis.[6] Thromboprophylaxis itself is not without risk, with rates of bleeding events in pedi-

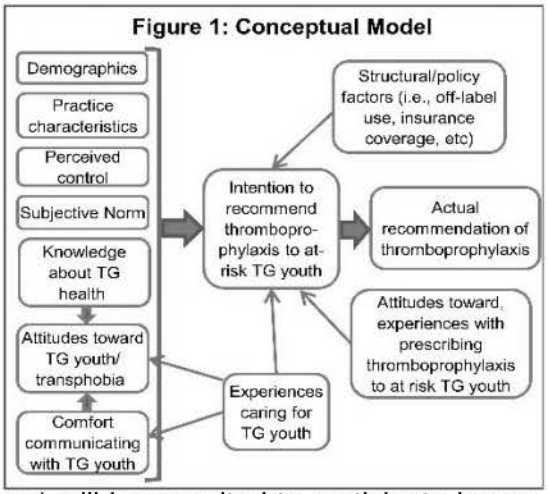
atric patients receiving low molecular weight heparin for primary prevention of thrombosis of 2.3% for clinically significant bleeding and 16.4% for minor bleeding.[133] *Because thromboprophylaxis carries its own risks, understanding the factors influencing recommendations to start prophylaxis for TG men is important to minimize risk.*

Clinician attitudes and behaviors toward TG patients impacts provision of clinical care and the health-seeking behaviors of TG patients. Historically, clinicians reported moderate to high levels of transphobia,[134] and higher degrees of transphobia are associated with lower willingness to provide routine medical care to TG people.[135,136] For example, a sizable minority of primary care and women's health clinicians were not willing to provide routine care to TG people (11% and 25%, respectively) or pap testing (21% and 15%, respectively).[135,136] TG youth reported avoiding medical care following experiences in which they were referred to by their non-affirmed gender and/or their non-affirmed pronouns, and such youth report experiencing a range of negative emotions after such encounters, including fear for their safety.[137] Gaps in clinician knowledge about care of TG people[138] and failure to use affirmed names and pronouns create barriers to care.[138,139] Physicians and other clinicians report low knowledge[140] and little professional training in this area,[134,141] while also recognizing the need for more training[140] and sensitivity in communicating with TG patients.[140,141] Less transphobia was associated with greater TG healthcare knowledge among primary care providers,[142] and positive experiences with clinicians[137,143] can improve access to care for TG patients. *Because clinical care is impacted by sensitivity in communication and transphobia (which is related to knowledge about TG health), assessing knowledge and attitudes of hematologists toward caring for TG youth is needed to support provision of gender-affirming care.*

A mixed-methods approach is well suited to understanding the attitudes and practices of clinicians with respect to a biomedical prevention medication. In areas of research for which little to no information is known, beginning with qualitative research methods allows for exploration and development of an in-depth, nuanced understanding of the topic,[125] such as the attitudes and practices of hematologists toward thromboprophylaxis for TG youth. Our team used a similar research strategy to understand a similarly unstudied area: biomedical prevention of HIV infection. We conducted two separate mixed-methods studies using the methodology in this proposal: starting with qualitative methods, then using those data to develop and disseminate surveys designed to produce generalizable data.[27,28,31,32,73] Our qualitative studies yielded previously unreported perceived barriers to providing oral medication for HIV prevention from physicians who care for youth.[28,31] Using these novel insights, we developed and disseminated surveys to samples of physicians caring for youth to generate generalizable data.[32,73] *Thus, our research team has the expertise in qualitative research and survey development/dissemination to successfully conduct this study aim.*

III.C.2. Phase 1 Qualitative Interviews

Individual semi-structured interviews will be conducted with a regional sample of pediatric and adult hematologists who care for youth. Qualitative research methods will allow us to capture the range of salient attitudes and practices toward evaluating and recommending thromboprophylaxis for TG youth receiving GAHT who are at risk for thrombosis due to personal or family risk factors. The exploratory hypothesis is that greater perceived benefits of GAHT will be associated with intention to recommend thromboprophylaxis to at-risk TG youth. The preliminary conceptual model developed using behavioral theory and our prior work is shown in **Figure 1.**[28,31,32,144] Specific constructs included within each model concept are shown in **Table 6.**



III.C.2.a. Subjects and Recruitment: Fifteen to 20 pediatric or adult hematologists who care for youth (ages 22 years and younger) will be recruited to participate in one-time individual interviews. Participants will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing TG care to youth (CCHMC, Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for TG youth at increased risk of thrombosis or who have had thrombosis. Invitations to the study will be sent to the business e-mail address of potential participants every 3 weeks. If no response is received after 3 attempts, the person will be removed from the recruitment list and an alternate will be contacted. Participants will receive $100 in compensation for their time.

III.C.2.b. Data Collection: Individual semi-structured interviews lasting about 60 minutes will be conducted by a single interviewer (PI) by online video using the Zoom platform. Informed consent will be obtained. Individual interviews will be conducted because they facilitate the discussion of sensitive topics (such as a physician's practices), and such interviews allow in-depth exploration of the factors influencing decisions about rec-

ommending thromboprophylaxis for TG youth with personal/family risk factors for thrombosis. Interviews will be recorded; audio files will be transcribed by an independent transcriptionist. Proposed interview items are shown in **Table 6**. **Appendix 1** shows the draft interview, which will be modified as needed to reflect up-to-date guidelines. A summary of existing data (i.e., thrombosis incidence, the limited data on coagulation changes) will be provided during the interview,[6,25,26,46] after which changes in attitudes will be assessed. Theory-based constructs are derived from the Theory of Planned Behavior (TPB), a well-established model of health-related behavior[144] that has been used successfully to examine other prevention-focused physician behaviors, including immunization practices[145-148] and recommending/prescribing HIV pre-exposure prophylaxis.[28,31,32] The TPB proposes that the strongest predictor of behavior is intention to perform the behavior; studies validate that intention is closely related to actual physician behavior.[149-151] Actual practices related to prescribing thromboprophylaxis to TG youth will be assessed. However, intentions are the primary outcomes because we expect that some hematologists may not yet have cared for TG youth, as published studies show that 50% of primary care providers have not cared for a TG patient in the last 5 years.[135,136] Although our prior work found that recommendation and prescription of HIV prevention medication were two different constructs for clinicians (e.g., a clinician might recommend medication but not be willing to prescribe it),[28,31,32] we expect that recommendation and prescription of thromboprophylaxis are likely to be the same construct for hematologists. To evaluate this assumption, we will include interview questions to assess intentions related to recommendation and prescription of thromboprophylaxis separately.

Table 6: Interview Content

Model Concept	Specific Constructs
Demographics	Age, Race, Medical Specialty Year graduated medical school State of fellowship (or highest level) of training
Practice characteristics, Transgender (TG) Patients	Number of adolescents (ages 13-17) seen per week Number of young adults (ages 18-22) seen per week Provided medical care in past to TG adolescent, young adult Number of TG adolescents, young adults in practice
Knowledge about TG health	Previous training on health care for TG youth or adults Familiarity with gender transition process Understanding of gender-related terms
Comfort communicating with TG youth, Attitudes toward TG youth	Comfort providing care to TG youth Comfort discussing gender, preferred name, pronouns Experiences providing care to TG adolescents, young adults Interventions to improve comfort providing care to TG youth
Experiences with thromboprophylaxis for TG youth	Experiences recommending, prescribing thromboprophylaxis to TG adolescents/young adults, factors leading to recommendations, medication used, goals of treatment
Theory-Based Predictors: Theory of Planned Behavior (TPB)	Attitudes • Attitudes toward gender-affirming hormone therapy • Behavioral beliefs (outcomes of giving thromboprophylaxis) • Attitudes toward recommending thromboprophylaxis for adolescents, young adults starting estrogen GAHT • Attitudes toward recommending thromboprophylaxis for adolescents, young adults starting testosterone GAHT • Attitudes toward which youth are at increased risk of thrombosis, recommended evaluation • Attitudes toward which patients should not start GAHT • Barriers/facilitators for recommending thromboprophylaxis Subjective Norms: Normative beliefs, Motivation to comply Perceived control to recommend thromboprophylaxis
Structural/Policy Factors	Cost, coverage by insurance Off-label use Guidelines from relevant influential organizations
Intentions (TPB)	Intention to recommend, prescribe thromboprophylaxis to TG adolescent at risk of thrombosis starting estrogen, testosterone Intention to recommend, prescribe thromboprophylaxis to TG young adult at risk of thrombosis starting estrogen, testosterone

III.C.2.c. Analytic Plan and Sample Size: Two members of the research team with expertise in qualitative data analysis (T. Mullins, (b)(6)) will review interview transcripts using a framework analysis approach (a 5-step method to analyze data and produce a conceptual framework).[152,153] After individual review, the team will meet to reach consensus regarding important themes. We will plan for approximately 15-20 interviews to meet sample size recommendations for qualitative interview studies seeking to achieve maximum variation.[154] However, we will maintain flexibility in total number of interviews in order to reach informational redundancy.

III.C.2.d. Expected Outcomes: The findings will provide novel insights into the range of attitudes and practices of hematologists related to determining which patients starting GAHT are considered at higher risk of thrombosis and those who would be considered for thromboprophylaxis, which is critical to the provision of informed consent to patients and families. The findings will also inform development of the survey below.

III.C.2.e. Potential Problems and Alternative Strategies:

a) Insufficient recruitment: We do not expect this to be an issue due to the established relationships between the target institutions through the (b)(6) There are at least 45-50 physicians specializing in hematology between the 4 target institutions.

b) Response bias: Physicians may alter their responses to interview questions to provide answers that they consider to be normatively acceptable. To minimize this type of bias, individual private interviews will be conducted, thereby ensuring confidentiality, and questions will be phrased to minimize implied judgment.

c) Potential participant fatigue: Interviews will be as succinct as possible. Should early interview participants demonstrate fatigue, questions about demographics and practice characteristics will be provided as self-administered questionnaires to be completed separate from the scheduled interview. The team has experience with physician interviews and feels confident that these domains can be assessed in the time frame described.

III.C.3. Phase 2 Survey Development: Cognitive Interviewing and Pilot Testing

III.C.3.a. Overview: Participants will include regional pediatric and adult hematologists who care for youth; they will be recruited as detailed for Study 1.

III.C.3.b. Measures: A survey informed by the Phase 1 qualitative findings will be developed to assess the domains detailed in **Table 6**. The inclusion of salient constructs that emerge from the qualitative data and

theory-based constructs will ensure that the survey ascertains the full range of relevant attitudes and actual and intended practices around prescribing thromboprophylaxis. Data from Aim 1 will be used to generate items assessing the influence of personal/family risk factors for thrombosis and laboratory test results on decisions about thromboprophylaxis. We expect that 5-10 items will be generated for new attitudinal scales. Established scales will be used to assess self-efficacy for interactions with TG patients (6 items; developed for helping professionals)[155] and transphobia (8 item adaptation of the New Transphobia Scale[156] used among health care professionals[142]). Other transphobia scales exist but have key limitations for this study (i.e., Genderism and Transphobia Scale includes inciting language and references to physical violence[157-159]; Attitudes Toward Transgendered Individuals scale includes out-of-date terminology and cross-dressing[160,161]; Attitudes toward Transgender Men and Women does not include attitudes toward non-binary people and has only been validated in undergraduate students[160]). Our prior studies show that clinician intentions to recommend and prescribe medication vary by whether the patient is an adolescent (age <18 years) or a young adult (18 years and over).[28,31,32] Therefore, the *primary outcomes* are intentions to recommend thromboprophylaxis to 1) a TG adolescent (age 13 to 17 years) starting estrogen GAHT, 2) a TG adolescent starting testosterone GAHT, 3) a TG young adult (age 18 to 22 years) starting estrogen GAHT, and 4) a TG young adult starting testosterone GAHT, at higher risk of thrombosis. Content validity will be established through use of theory, literature review, and expert review.

III.C.3.c. Cognitive Interviewing is a process during which potential participants provide interpretations of the survey questions and responses and will be the first method used to ensure that survey items are clear.[162] Cognitive interviews will be done with 5 hematologists; we will maintain flexibility to conduct a second round of 5 interviews depending on the findings of the first round.[163] Participants will receive $100 in compensation for their time. Interviews will last about 60-90 minutes and be conducted over Zoom by the PI, who has formal training and experience with this method. Participants will be asked to read and talk aloud as they interpret each question and the possible responses. Audio recordings of interviews will be transcribed by an independent transcriptionist. The PI will take field notes during the interview. Analysis: Transcripts will be compiled with field notes to systematically analyze responses, with the item as the unit of analysis.[164] Items will be modified based on participant comments related to clarity, wording, applicability, or tone[165] or if multiple competing interpretations are received.[165] The team will review potential changes to reach consensus about how to implement changes.

III.C.3.d. Pilot Testing: Pilot testing will be done by the PI via Zoom with 5-10 hematologists.[163] Because the final survey will be administered online, pilot surveys will be online. Participants, who will receive $50, will be asked to provide comments regarding question clarity. Analyses for pilot testing include descriptive statistics (e.g. mean, median, standard deviation, range, frequencies) and examination of missing data. The distribution of responses will be scrutinized for floor and ceiling effects.[166] Items with >10% missing data or highly skewed distributions will be revised. Although our small sample for pilot testing impairs our ability to perform factor analysis, we will examine correlation coefficients for scale items in order to assess construct validity at this stage.[167] Construct reliability and validity will be further examined using the nationally disseminated survey.

III.C.3.e. Potential Problems and Alternative Strategies:

a) Insufficient recruitment for survey development: If we are unable reach recruitment targets, we will recruit additional hematologists who care for youth ages 13-22 years from adult hospitals affiliated with the pediatric institutions that are part of the (b)(6)

b) Participant fatigue: Surveys will be as succinct as possible. The team has experience with conducting cognitive interviews and pilot testing and feels confident that these can be assessed in the time described.

III.C.4. Phase 3 Survey Dissemination

The newly developed survey will be disseminated to a sample of U.S. and Canadian pediatric and adult hematologists. We hypothesize that greater perceived benefits of GAHT will be associated with intention to recommend thromboprophylaxis to TG youth with increased risk of thrombosis due to personal or family risk factors.

III.C.4.a. Subjects and Recruitment: A sample of U.S. and Canadian pediatric and adult hematologists will be recruited through the Hemostasis and Thrombosis Research Society (HTRS) and the American Society of Pediatric Hematology/Oncology (ASPHO). HTRS members are North American health care professionals with interests in hemostatic and thrombotic disorders. In 2020, HTRS had 261 doctoral-level faculty members and 171 trainee members (who transition to faculty membership after training). In ASPHO, 61% of members are pediatric hematologists or hematologists/oncologists (n=1220). Inclusion criteria include physicians practicing hematology in the U.S. or Canada, ability to understand written English, and providing hematologic care to adolescents and/or young adults (any patients aged 13-22 years). Participants will receive a $20 mailed gift card in compensation for their time. Such modest incentives serve as a token of appreciation and respect for the physician's time and have been shown to increase survey response rates among physicians.[168]

III.C.4.b. Survey Administration: Surveys will be online, following established methods to maximize

completion.[169,170] Emails including a cover letter detailing the purpose of the survey and the survey link will be sent to the business email address of members of HTRS by HTRS and by study staff for ASPHO members. A reminder email with the survey link will be sent 2-3 weeks later, with a third reminder 2-3 weeks thereafter.[171]

III.C.4.c. Analytic Plan: The *primary outcomes* are intentions to recommend thromboprophylaxis to a TG 1) adolescent (age 13-17 years) starting estrogen GAHT, 2) adolescent starting testosterone GAHT, 3) young adult (18-22 years) starting estrogen GAHT, and 4) young adult starting testosterone GAHT, who have personal and/or family risk factors for thrombosis. Similar to prior studies assessing physician intentions toward providing preventive services,[32,73,146,172,173] intentions will be measured as scales. For each outcome, we will assess intentions related to several patient categories to capture differences in intentions related to various risk factors **(Table 7).** Categories may be modified based on our qualitative and Aim 1 results. Each intention item will be measured on a 5-point Likert-type scale; higher scores indicate greater intention to recommend prophylaxis. Mean scale scores will be calculated and examined for normality. If mean scale scores are highly skewed, outcomes will be dichotomized for analysis into greater intention (very/somewhat likely to recommend) vs. lower intention (neither, somewhat/very unlikely), as in other studies of intentions.[32,174-178]

Table 7: Assessment of Intentions Toward Thromboprophylaxis

1. How likely or unlikely are you to recommend thromboprophylaxis to a transgender adolescent (age 13-17 years) starting estrogen GAHT with:
   a) obesity (BMI>95th percentile for age)?
   b) personal history of thrombosis?
   c) first-degree family member with thrombosis?
   d) elevated Factor VIII level?
   e) heterozygous Factor V Leiden?
   f) PAI-1 gene polymorphism?

a. The categories of patient (a-f above) will remain constant across all outcomes but the stem of the question will change:

2. How likely or unlikely are you to recommend thromboprophylaxis to a transgender adolescent starting testosterone GAHT....

3. How likely or unlikely are you to recommend thromboprophylaxis to a transgender young adult (age 18-22 years) starting estrogen GAHT...

4. How likely or unlikely are you to recommend thromboprophylaxis to a transgender young adult starting testosterone GAHT...

III.C.4.c.i. Descriptive statistics will be used to examine demographics, practice characteristics, knowledge about TG health, transphobia, comfort communicating with TG youth, experiences with evaluation/management of thromboprophylaxis for TG youth, attitudes, and other theory-based predictors, and proportions of physicians who intend to recommend thromboprophylaxis to adolescents and young adults with personal and/or family risk factors for thrombosis starting estrogen or testosterone GAHT. The distribution of response outcomes will be assessed.

III.C.4.c.ii. Analysis of attitudinal scales will include confirmation of subscale composition using confirmatory factor analysis,[167] examining correlations between scale items to determine whether items are related to one another, suggesting that they measure the same construct. Exploratory factor analysis using scale scores will be used to assess for convergent and discriminant validity.[179] Internal consistency reliability of scales will be assessed through computation of Cronbach's alphas to ensure the factor analysis has identified cohesive subscales that identify single underlying constructs. Items in scales with unacceptable Cronbach's alpha scores (<0.50) will be analyzed individually.[180] Mean scale scores will be computed.

III.C.4.c.iii. Univariate analyses will examine associations between predictor variables (demographics, practice characteristics, knowledge about TG health, transphobia, comfort communicating with TG youth, experiences with evaluation and management of thromboprophylaxis for TG youth, attitudes, and other theory-based predictors) and the primary outcomes: intentions to recommend thromboprophylaxis to 1) a TG adolescent starting estrogen GAHT, 2) a TG adolescent starting testosterone GAHT, 3) a TG young adult starting estrogen GAHT, and 4) a TG young adult starting testosterone GAHT, who have personal/family risk factors for thrombosis. We will use linear regression modeling if the outcome scale scores are normally distributed and analyzed as continuous variables or logistic regression modeling if the scores are skewed and dichotomized for analysis.

III.C.4.c.iv. Multivariable regression models will be estimated to determine variables independently associated with the primary outcomes. Linear regression modeling will be used if the mean scale scores for outcomes are normally distributed and analyzed as continuous variables. Logistic regression modeling will be used if the scores are skewed and thus dichotomized for analysis. We will estimate 4 separate models for the primary outcomes: intentions to recommend thromboprophylaxis to 1) a TG adolescent starting estrogen GAHT, 2) a TG adolescent starting testosterone GAHT, 3) a TG young adult starting estrogen GAHT, and 4) a TG young adult starting testosterone GAHT, who have personal and/or family risk factors for thrombosis. Predictor variables associated with an outcome at $p<0.10$ on univariate analyses will be entered as independent variables into the regression model for that outcome. A p-value of <0.05 will be considered significant in the final multivariable models. We will use Fisher's protected least significant difference to control for multiple comparisons. Also, we will examine correlations between outcomes, and if highly correlated, use multivariate regression modeling, which accounts for the correlation between multiple outcomes in order to reduce standard and type I errors.[181,182]

III.C.4.d. Sample Size: The sample size of 370 was determined by a series of power calculations, including adjustments for response rate.[183] Surveys administered through the proposed subspecialty networks have achieved response rates of 29-47% (without reported incentives),[128,184,185] similar to surveys targeting other subspecialty networks of physicians.[186-189] Because response rate improves with increasing topical relevance to respondents[163,190] and incentives will be provided for the current study, we anticipate a response rate of 45%.We

estimate that 80% of survey recipients will meet eligibility criteria.[191,192] We estimate that 40% of hematologists would intend to prescribe thromboprophylaxis to outpatient TG youth on GAHT, based on a prior study reporting that 68% of pediatric hematologists would consider recommending pharmacologic thromboprophylaxis to critically ill hospitalized adolescents using oral contraceptive pills, and 72% would recommend such treatment to critically ill adolescents with other risk factors for thrombosis.[128] Because there are inconsistent data on use of exogenous testosterone, [25,26,129-132] we powered this study to detect differences in intention to prescribe thromboprophylaxis to youth using estrogen GAHT. Sample size calculation was based on two sample t-test to detect the difference in mean transphobia score between respondents reporting higher intention vs. lower intention to prescribe thromboprophylaxis to youth at higher risk of thrombosis on estrogen GAHT. We assumed a 1:1.5 sample allocation (40% with higher intention vs. 60% with lower intention), which is similar to physician intentions to prescribe HIV prevention medication.[31] A sample size of 133 completed surveys (53 in higher intention group and 80 in lower intention group) achieves 81% power to detect a difference of 1 point in mean transphobia score (mean score of 3 in higher intention vs. 4 in lower intention group) with standard deviation of 2 and significance level (alpha) of 0.05 using a two-sided two-sample t-test. Thus, a total of 370 surveys (x 45% response rate x 80% eligibility) will be sent to guarantee a sufficient number of completed surveys. Linear and logistic regression modeling require 10-15 cases per variable to ensure adequate power for the analysis;[193] thus, our sample size provides adequate power for inclusion of at least 8 covariates in the final multivariable regression model.

III.C.4.e. Expected Outcomes: The findings will provide novel insights into which youth are considered by hematologists to be at increased risk of thrombosis; what evaluation should be undertaken; and to which youth hematologists intend to recommend thromboprophylaxis and the factors associated with these intentions. This information is critical for physicians, patients, and families as they weigh the risks and benefits of GAHT to provide informed consent for this intervention and for hematologists who are evaluating patients for possible thromboprophylaxis. These findings will also be critical to the design of educational materials for patients and families, as well as the development of clinical guidelines for hematologic care of TG youth at risk of thrombosis.

III.C.4.f. Potential Problems and Alternative Strategies:

a) Low response rate: To maximize our response rate, we will ensure brevity of the survey and provide a monetary incentive.[170,194] Studies suggest that a smaller incentive, such as $20 gift card, is the most cost-effective way to maximize responses to physician surveys,[195,196] and a promised incentive increases the response rate (as opposed to lotteries).[163,197] Surveys administered through the proposed subspecialty networks have achieved response rates of 29-47% (without reported incentives).[128,184,185] In the unlikely event that our response rate is low (i.e. <40%), we will recruit using provider lists through the American Medical Association.

b) Missing data/incomplete surveys: Surveys with ≥75% of scale items completed will be included in analysis.[198] Missing data for such scales will be imputed based on responses to the majority of scale items.

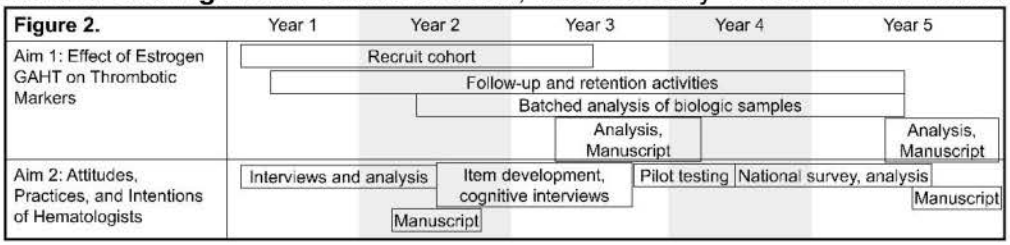
c*) Changes in guidelines/approval*: If new relevant clinical guidelines are released or the FDA approves use of an agent for thromboprophylaxis among TG youth, we will modify the interviews or surveys accordingly.

d) Skewed outcomes: Data transformation will be used as an alternative for skewed outcomes scores.

III.C.5. Scientific Rigor: Use of rigorous, established, complementary[199,200] qualitative and survey research methods allows an in-depth understanding of the attitudes and intentions of hematologists toward prescribing prophylaxis to TG youth at risk of thrombosis. Using qualitative results to develop items ensures inclusion of key constructs that might otherwise be missed,[199,200] coding by multiple team members minimizes risk of bias, and cognitive interviewing and pilot testing ensure that survey items are clear and capture the intended information.

IV. Study Timeline: See Figure 2. For further detail, see the Study Timeline in the Human Subjects section.

Figure 2.



V. Future Directions and Scientific Priorities: Building upon this study, we will design a future NIH application to develop and pilot an intervention targeting physicians caring for TG youth to improve knowledge of thrombosis risk with GAHT and inform evidence-based referral of youth for hematologic assessment prior to GAHT. Future work also includes developing a clinical tool to aid in referral and evaluation of youth at risk for thrombosis, as well as examining changes in thrombotic factors associated with testosterone GAHT, particularly if our findings suggest high rates of recommendation of thromboprophylaxis by hematologists nationally for such youth.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 02/28/2023

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *	● Yes ○ No
Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.	
Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Aim 1: Thrombosis Risk in Young Transgender Women	No
2	Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth	No
3	Aim 2.2a: Cognitive Interviews for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth	No
4	Aim 2.2b: Pilot Testing for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth	No
5	Aim 2.3: Survey of Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

Aim 1: Thrombosis Risk in Young Transgender Women

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

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

1.4. Clinical Trial Questionnaire *

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

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

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- - Transgender persons
- - Gender dysphoria
- - Gender identity
- - Adolescent
- - Young adult
- - Thrombosis
- - Risk factors
- - Blood coagulation tests
- - Longitudinal studies

2.2. Eligibility Criteria

Inclusion criteria:
- Diagnosed with gender dysphoria
- Clinical care at the Cincinnati Children's Hospital Medical Center Transgender Health Center
- Initiation of estradiol gender-affirming hormone therapy
- Age ≤22 years at start of gender-affirming hormone therapy
- Able to understand written and spoken English

Exclusion criteria:
- Personal history of thrombosis
- Personal history of bleeding disorder
- Personal use of anticoagulation during gender-affirming hormone therapy (except standard of care around surgery)
- Inability to comply with study procedures or provide consent/assent
- Ward of the state

2.3. Age Limits	Min Age: N/A (No limit)	Max Age: 22 Years
2.3.a. Inclusion of Individuals Across the Lifespan	Inclusion_across_Lifespan_Aim_1_Thrombosis_Ris.pdf	
2.4. Inclusion of Women and Minorities	Inclusion_of_Women_and_Minorities_Aim_1.pdf	
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Aim_1_Thrombosis_Ris.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	Study_Timeline.pdf	
2.8. Enrollment of First Participant	10/01/2022	Anticipated

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN

Specific Aim 1: In a population of transgender women (up to age 22 years at gender-affirming hormone therapy start), prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen gender-affirming hormone therapy.

For Aim 1, we propose to recruit transgender and gender nonconforming youth up to and including age 22 years at the time of starting estrogen for gender-affirming hormone therapy. We do not include a lower age limit because the timing of start of gender-affirming hormone therapy may be different for different participants. Although the median age for starting estrogen was 18 years (with interquartile range of 16-20 years) in our retrospective cohort,[6] the youngest age was 13 years, which was the youngest age for inclusion in the study cohort. There is no recommended minimum age for the initiation of gender-affirming hormone therapy.[13] The current treatment guidelines recommend that decisions about starting gender-affirming hormone therapy "be made among the adolescent, the family, and the treatment team."[13] Defining the upper age limit of 22 years (with 2 years of follow-up) will allow us to capture this critical information for the entire span of adolescence and early adulthood as defined by Healthy People 2020,[205] particularly as younger adults often make up only a small proportion of participants in studies of transgender adults.[26,132,206-209]

Dr. T. Mullins (PI), (b)(6) (co-I), (b)(6) (collaborator), and (b)(6) (collaborator and (b)(6) of the Transgender Health Clinic at Cincinnati Children's Hospital Medical Center) are all board-certified pediatric physicians. Drs. T. Mullins, (b)(6), and (b)(6) all practice in the subspecialty of adolescent medicine and provide general care to transgender youth. Dr. T. Mullins, (b)(6), and (b)(6) all provide consultative care to transgender youth and young adults in the age range proposed for participants. The Transgender Health Clinic is housed within Cincinnati Children's Hospital Medical Center, one of the top four pediatric hospitals in the U.S. (U.S. News and World Reports); all facilities at this institution provide appropriate care for the proposed age range.

INCLUSION OF WOMEN AND MINORITIES

Specific Aim 1: In a population of transgender women (up to age 22 years at gender-affirming hormone therapy start), prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen gender-affirming hormone therapy.

In Aim 1, we plan to recruit transgender and gender nonconforming youth who are using estrogen for gender-affirming hormone therapy; these participants will have been assigned male sex at birth and are using estrogen for feminization to achieve their affirmed (self-identified) gender. As described in the significance and approach sections of this proposal, estrogen has a well-documented prothrombotic impact on coagulation factors in cisgender women (women who were assigned female sex at birth) using hormonal contraception[21,22] and hormone replacement therapy.[23,24] Multiple studies have also demonstrated an increased risk of venous thromboembolism and stroke among transgender women using estrogen for gender-affirming hormone therapy.[25,26,208,210] In contrast, there is no consistent data about an association between use of exogenous testosterone for gender-affirming hormone therapy by people assigned female sex at birth (who are using testosterone for masculinization) and risk of thrombosis. In retrospective studies of gender-affirming hormone therapy in adult transgender men, testosterone appears to have minimal risk for both venous thromboembolism and stroke.[25,26,132] Therefore, based on the literature demonstrating increased risk of thrombosis and prothrombotic changes in the hemostatic system associated with use of estrogen – but not testosterone – we are limiting recruitment to youth who are using estrogen for gender-affirming hormone therapy (youth who were assigned male sex at birth).

We do not anticipate targeted recruitment based on minority status, and no minority will be excluded from the study. Based on the findings of our team's retrospective review of all patients starting gender-affirming hormone therapy through the Cincinnati Children's Hospital Medical Center Transgender Health Clinic, we expect that participants will be 89.4% white, 8.5% Black/African-American, 1.3% Asian, 0.5% Native Hawaiian/Pacific Islander, 0.3% American Indian/Alaska Native. We estimate that 2.3% of participants will be Hispanic/Latino.[6]

RECRUITMENT AND RETENTION PLAN

Specific Aim 1: In a population of transgender women (up to age 22 years at gender-affirming hormone therapy start), prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen gender-affirming hormone therapy.

I. RECRUITMENT PLAN

Recruitment location

Participants will be recruited from the multidisciplinary Transgender Health Clinic (THC) in the Division of Adolescent and Transition Medicine at Cincinnati Children's Hospital Medical Center (CCHMC). Founded in July 2013, the Transgender Health Clinic provides gender care to adolescents and young adults from a four-state catchment area (Ohio, Kentucky, Indiana, West Virginia). Demand for care within this clinic has been high since its inception. In each of the last 3 years, approximately 300 new patients were seen in the clinic. Due to ongoing increase in demand, in FY 22, two additional clinicians joined the THC. On average, there are 12 half-day sessions each week (with 7-10 youth scheduled per session) dedicated to the care of transgender youth.

Patient characteristics and sample size

Seventy-five transgender or gender nonconforming youth (ages 22 years-old or younger) starting estrogen for gender-affirming hormone therapy will be recruited. Transgender men or gender nonconforming youth taking testosterone are not included in this study because testosterone for gender-affirming hormone therapy does not appear to be a significant risk factor for thrombosis.[25] Participants will be recruited prior to initiating gender-affirming hormone therapy and followed for 24 months from the start of gender-affirming hormone therapy. Accounting for attrition rates and participants being lost to follow-up, we anticipate that enrolling 75 participants will yield longitudinal data for at least 60 participants, as is required based on sample size calculations (detailed in "Approach"). Prior longitudinal cohort studies (lasting 12-18 months) of transgender women[7] and sexual and gender minority youth[8] achieved retention rates of over 90%. Participants will receive $100 at each completed in-person study visit (baseline prior to hormone start, and then at 3, 6, 12, 18, and 24 months after hormone start) and $25 for each completed telephone study visit (at 9, 15, and 21 months after hormone start) in compensation for their time. This is consistent with the compensation strategy of an ongoing longitudinal study examining the psychosocial impact of hormone therapy for transgender and gender nonconforming youth.[213]

Sampling strategy

Participants will be recruited directly from patient visits with the Transgender Health Clinic by a trained clinical research coordinator (CRC), who will also conduct study visits and interim follow-up phone calls in order to foster connection of participants with study staff. Patient visits with Transgender Health Clinic clinicians are conducted both in-person and by telehealth. Clinic schedules will be reviewed in advance by the CRC to identify potentially eligible participants. The study team will also regularly meet with Transgender Health Clinic staff in order to anticipate which patients might be starting estradiol gender-affirming hormone therapy. For patients seen for in-person visits, the CRC will meet with the potential participant and their accompanying parent/legal guardian to introduce the study. Participants who consent (or if under age 18 years, assent with parent consent) to the study will have the baseline study procedures conducted at that time (or scheduled to be done prior to starting hormone therapy). For patients who are seen for telehealth visits, the CRC will meet briefly with the potential participant to introduce the study, and then an in-person visit will be scheduled to perform assent/consent procedures and conduct the baseline study visit (per CCHMC institutional policy, study visits cannot be conducted using telehealth resources).

Modes of recruitment

Multiple modes of recruitment will be used:

1) Direct recruitment by a research coordinator during clinic sessions (both in-person and telehealth) to meet with interested potential participants about the study. For participants recruited from in-person clinic visits, the baseline study visit may be conducted on the day of recruitment (following completion of assent/consent procedures) or scheduled for another day based on participant and family preference. For participants recruited from telehealth clinic visits, baseline study visits (including assent/consent procedures) will be scheduled.

2) Flyers listing contact information for study personnel will be posted in the Transgender Health Clinic clinical space.

In 2019 alone, 62 patients receiving care in the Transgender Health Clinic initiated estrogen for gender-affirming hormone therapy. Given the consistent increase in demand since that time and the recent expansion of services in the Transgender Health Clinic, there are sufficient numbers of patients from which to recruit. We estimate that it will take 24-27 months to reach full recruitment of the cohort.

II. RETENTION PLAN

In order to maximize retention over the course of the study, several strategies will be used, with particular attention paid to strategies that have been reported to be critical to the recruitment and retention of cohorts of transgender and gender nonconforming people.

1) At the time of recruitment and at each point of contact with participants, we will collect contact information for participants (phone number[s], mailing address, email address) and for one family member who is aware of the participant's gender identity and participation in the study to serve as a contact person (name, phone number).[214,215]

2) We will verify preferred name and pronouns with participants at each point of contact.[214,215]

3) The goals and intended use of the research, as well as the importance of completion of all study procedures and visits to the success of the research, will be discussed at the time of enrollment and again at each point of study contact.[214-216] Participants and their parents/legal guardians will also be thanked for their participation at each point of contact.

4) Participants will be provided with information on how to contact the study team in the event of a change in contact information.

5) The next study visit will be scheduled at the current study visit (for example, the 3-month study visit will be scheduled at the baseline visit, etc.).

6) Participants will be asked about how they prefer to be reminded about upcoming study visits (telephone call, mailed physical reminders, email contact, etc.). We will also specifically ask the participant who study staff may speak with and the name for the participant (chosen or birth name) and pronouns that should be used with that person.[214,215] The parent or legal guardian similarly will be asked preferred mode of contact. Reminder contact will be made 2-3 days in advance of scheduled visits for phone or email reminders, and 7-10 days in advance of study visits for physically mailed reminders. All contacts will be carefully crafted to minimize breach of confidentiality (for example, avoiding use of gender terms).

7) Contact with participants (via their preferred mode of contact) will be made 1-2 weeks after each study visit to thank participants for their participation and include a reminder to participants to contact the study team with any changes to their contact information.

8) Follow-up study visits will be scheduled in coordination with Transgender Health Clinic visits when possible.

9) A quarterly study newsletter detailing progress of the study, general health information relevant to adolescents, etc. will be disseminated via the participant's most recently reported preferred mode of contact and with the most recently reported preferred name for making contact. Newsletters will be carefully crafted to minimize breach of confidentiality (for example, avoiding use of gender terms). Participants will be provided an option to opt out of this contact.

10) Birthday cards will be sent via the participant's most recently reported preferred mode of contact and with the most recently reported preferred name for making contact. Cards will be carefully crafted to minimize breach of confidentiality (for example, avoiding use of gender terms). Participants will be provided an option to opt out of this contact.

11) CCHMC provides free parking for patients and families accessing services on campus.[214]

STUDY TIMELINE

The research team will hold monthly in-person meetings to review progress and plan for upcoming work.

	Pre-award	Year 1				Year 2				Year 3				Year 4				Year 5			
Quarter		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Aim 1: Estrogen Gender-Affirming Hormone Therapy Effect on Thrombotic Markers																					
IRB submission	x																				
Preparation of recruitment materials		x																			
Staff training		x																			
Recruitment of cohort			x	x	x	x	x	x	x	x	x										
Follow-up visits and retention activities				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Batched analysis of biologic samples								x	x	x	x	x	x	x	x	x	x	x	x		
Data analysis											x	x						x	x	x	x
Manuscript preparation												x	x						x	x	x
Aim 2: Attitudes and Intentions of Hematologists																					
IRB submission	x																				
Staff training		x																			
Phase 1: Conduct interviews			x	x	x	x															
Phase 1: Analyze interviews				x	x	x	x														
Phase 2: Item development								x	x												
Phase 2: Conduct cognitive interviews										x	x										
Phase 2: Analyze cognitive interviews and revise items, further cognitive interviews (if needed)											x	x									
Phase 2: Pilot testing, analysis, and item revision													x	x	x						
Phase 3: Disseminate national survey															x	x	x				
Phase 3: Analysis of national survey data																		x	x		
Manuscript preparation							x	x												x	x

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	Hospital

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : Aim 1: Thrombosis Risk in Young Transgender Women

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): Hospital

6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	6	0	0	0	6
White	65	0	2	0	67
More than One Race	1	0	0	0	1
Total	73	0	2	0	75

Cumulative (Actual)

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

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	Human_Subjects_Aim_1_Thrombosis_Risk.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	DSMP_Aim_1_Thrombosis_Risk_in_Young_TG_Women.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	

PROTECTION OF HUMAN SUBJECTS

Specific Aim 1: In a population of transgender women (up to age 22 years at gender-affirming hormone therapy start), prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen gender-affirming hormone therapy.

Risks to Human Subjects

Human Subjects Involvement and Design

Participants will be recruited from the multidisciplinary Transgender Health Clinic in the Division of Adolescent and Transition Medicine at Cincinnati Children's Hospital Medical Center (CCHMC). We will recruit 75 individuals 22 years-old or younger starting estrogen for gender-affirming hormone therapy. Individuals will be recruited prior to initiating estrogen for gender-affirming hormone therapy and followed for 24 months from initiation of gender-affirming hormone therapy. Potential participants and their parent(s) or legal guardian(s) (for potential participants under age 18 years) will be approached about the study by a trained clinical research coordinator (CRC) during scheduled clinic visits in Transgender Health Clinic (in person or by telehealth).

Characteristics

Participants will be recruited from among transgender and gender-nonconforming youth who are receiving care in the Transgender Health Clinic and are initiating estrogen for gender-affirming hormone therapy. Inclusion criteria are: 1) age 22 years of age or younger at the start of gender-affirming hormone therapy; 2) diagnosed with gender dysphoria; 3) receiving clinical care at the CCHMC Transgender Health Clinic; 4) initiation of estrogen for gender-affirming hormone therapy; and 5) English-speaking. Exclusion criteria are: 1) personal history of thrombosis; 2) personal history of bleeding disorder; 3) personal use of anticoagulation during gender-affirming hormone therapy (except for standard of care use around surgery); 4) inability to comply with study procedures or provide consent/assent; and 5) ward of the state.

Study Procedures, Materials, and Potential Risks

Procedures

Participants will be recruited from the multidisciplinary Transgender Health Clinic (THC) in the Division of Adolescent and Transition Medicine at Cincinnati Children's Hospital Medical Center (CCHMC). Potential participants and their parent(s) or legal guardian(s) will be approached about the study by a trained clinical research coordinator (CRC) during scheduled clinic visits in THC (in person or by telehealth). A longitudinal cohort study will be performed with in-person visits at baseline (prior to starting estrogen gender-affirming hormone therapy), and then at 3 months, 6 months, 12 months, 18 months, and 24 months after starting hormone therapy. Interim telephone study visits will be conducted at 9 months, 15 months, and 21 months after starting hormone therapy. Participants will be recruited directly from patient visits with the THC by a trained CRC, who will also conduct in-person study visits and follow-up study phone calls in order to foster connection of participants with study staff. Patient visits with THC clinicians are conducted both in-person and by telehealth. Clinic schedules will be reviewed in advance by the CRC to identify potentially eligible participants. The study team will also regularly meet with THC staff in order to anticipate which patients might be starting estrogen gender-affirming hormone therapy. For patients seen for in-person visits, the CRC will meet with the potential participant and their accompanying parent/legal guardian to introduce the study. Participants who consent (or if under age 18 years, assent with parent consent) to the study will have the baseline study procedures conducted at that time (or scheduled to be done prior to starting hormone therapy). For patients who are seen for telehealth visits, the CRC will meet briefly with the potential participant to introduce the study, and then an in-person visit will be scheduled to perform assent/consent procedures and conduct the baseline study visit (per CCHMC institutional policy, study visits cannot be conducted using telehealth resources).

Materials

The research materials to be collected from human subjects include demographic data, health questionnaires, anthropometrics, blood samples, and banked blood samples. A study enrollment log containing the most updated contact information (including preferred mode of contact) will also be kept. Data will be entered by the CRC directly into the study database using Research Electronic Data Capture (REDCap) software, a HIPAA-

compliant online software program used by many academic research institutions. Data are password protected and only accessible to study personnel.

1. Demographic data: Demographic data will include verifying safe and preferred mode of contact with the participant/family and assessment of current gender identity and pronouns (as these can change over time). Demographics will be collected by the CRC at all in-person and telephone study visits. Administration of questionnaires by the CRC will allow for any clarifying questions to be asked to ensure that accurate data is collected. Data will be entered by the CRC directly into REDCap. Electronic data will be stored on a secure, limited-access network drive at CCHMC. Only study personnel will have access to the data.

2. Health questionnaires: Health questionnaires will include assessment of current hormone formulation, dosage taken, and adherence; use of other hormones than those prescribed from THC (i.e., obtained over the internet or additional hormones obtained from other clinicians); interim changes to personal or family history; other current medications; assessment of personal and family risk factors for thrombosis; and assessment of interval thrombosis. Health questionnaires will be verbally administered by the CRC at all in-person and telephone study visits. Personal health and family history questions will be asked of both the participant, and, for those under age 18, the parent/legal guardian who is aware that the participant is in the study. Administration of questionnaires verbally by the CRC will allow for any clarifying questions to be asked to ensure that accurate data is collected. Data will be entered by the CRC directly into REDCap. Electronic data will be stored on a secure, limited-access network drive at CCHMC. Only study personnel will have access to the data.

3. Anthropometrics: Anthropometrics (including height, weight, body mass index, blood pressure) will be obtained at all in-person study visits. Data will be obtained by the trained CRC or CCHMC Schubert Research Clinic nurse. All data will be entered by the CRC (who will be present for the entirety of each in-person study visit) directly into REDCap. Electronic data will be stored on a secure, limited-access network drive at CCHMC. Only study personnel will have access to the data.

4. Blood samples: Non-fasting blood samples will be drawn at each in-person study visit. Blood will be drawn by a trained phlebotomist, physician, licensed medical assistant, or nurse in the CCHMC Schubert Research Clinic. Samples will be used to assess hormone levels (estrogen and testosterone, sex hormone binding globulin), coagulation parameters, thrombophilia polymorphisms, and platelet activation as detailed in the "Approach." These will be analyzed by the CCHMC Clinical laboratory (with hormone labs sent to (b)(4) (b)(4) Division of Hematology – Hematology and Thrombosis Laboratory at CCHMC, and in (b)(6) (b)(6) s laboratory (see "Approach").

5. Banked blood and DNA samples: Participants will also be asked separately for assent/consent to participate in banking of their samples in a repository for future studies.

6. Enrollment and contact information log: In order to ensure that participants are enrolled only once and that participants are contacted by their desired mode of contact, a list of participants' names/contact information will be kept. All information will be stored on a secure, password-protected, limited-access network drive.

Potential Risks

We estimate that the risks of participation in this study are no greater than minimal risk and do not exceed those encountered during the performance of routine physical examination and testing (i.e., routine laboratory testing that is performed at visits with the Transgender Health Clinic to monitor response to hormone therapy). All participants will be assigned a unique study identification number that will be used in study databases. A separate password-protected file will link study identification numbers to patient names and medical record numbers. This file will be expunged at the close of the study. To further minimize risks and protect participants' confidentiality, all members of the study team will have completed mandated training procedures and certifications. Potential risks include:

1. Breach of confidentiality: For this population, the most significant risk is breach of confidentiality. This includes not only breach of confidentiality that the person is participating in the study, but also breach of confidentiality of their transgender or gender-nonconforming identity to others. Many youth have not disclosed their transgender or gender-nonconforming identity to family members or others in their social circles. Thus, while youth may present for clinic or study visits as their affirmed gender (the gender with which they identify) and using their preferred name and pronouns, youth may still be living in their birth gender or using their birth name and pronouns in other situations. The study team has worked closely with physicians caring for youth in the Transgender Health Clinic (including (b)(6)) to develop this protection of human subjects plan in order to ensure the highest level of protection possible against this risk.

2. Emotional distress: Participants may experience psychological distress or discomfort while answering questions about gender identity, pronouns, contact information, health questionnaires, or during anthropometric measurements.

3. Disclosure of suicidal ideation: Even though the study does not assess mood or suicidal ideation, there is a small risk that participants may disclose suicidal ideation.

4. Disclosure of new personal or family risk factors for thrombosis: New personal or family risk factors for thrombosis may be disclosed by the participant and/or parent/legal guardian.

5. Disclosure of additional hormone use not prescribed through the Transgender Health Clinic: Patients may access hormones from sources other than the Transgender Health Clinic, such as through the internet or other medical providers, with the intent of hastening the feminization process. Although routine lab monitoring of estrogen levels is done through the Transgender Health Clinic, such additional hormone use could impact clinical management of these patients.

6. Abnormal study test results: Abnormal test results may be obtained for study tests, including hormone levels, coagulation factors, thrombophilia polymorphisms, and platelet activation.

7. Blood sampling: Physical risks of the blood draw include bruising and slight discomfort (common). Fainting and infection are rare risks of the blood draw.

Adequacy of Protection Against Risks

Informed Consent

Prior to initiating the study, approval from the Institutional Review Board (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) will be obtained. CCHMC will serve as the IRB of record. All required elements of informed consent will be delivered as a written informed consent document provided and reviewed by the research staff with each potential participant and, for participants under the age of 18 years, their parent or legal guardian (hereafter "parent"). Wards of the state will be excluded due to significant concerns about the ability to protect confidentiality for this group. Youth under the age of 18 years cannot have a new visit in the Transgender Health Clinic without an accompanying parent, and parental consent from at least one parent is required for initiation of gender-affirming hormone therapy for youth under age 18 years. For youth under age 18 years, we will obtain participant assent and consent of one parent (because many youth have not disclosed their transgender or gender-nonconforming status to both parents and because the study is minimal risk). When youth turn 18 years-old, new informed consent documents will be obtained at the next in-person visit. Informed consent documents will note that the participant's care in the Transgender Health Clinic will not change based on participation in the study and that should a risk factor for thrombosis be uncovered, the patient would be referred for hematologic evaluation with the goal of continuing gender-affirming hormone therapy. This information will be specifically included in order to address concerns related to having gender-affirming hormone therapy interrupted, which could itself pose a substantial risk to the participant's mental health.

Protections Against Risk

1. Breach of confidentiality: Study participants will be assigned a study identification number for use in all study databases. A separate password protected file linking the participant's name and medical record number to the study identification number will be kept for the duration of the study and then expunged. At each contact (in-person or by phone) with the participant, study staff will confidentially obtain from the participant their preferred mode of contact (and which name to be used in such contacts), and who the study team can contact in the event of needing to discuss laboratory results or other urgent needs related to the participant's mental or physical health, as well as what name for the participant should be used with that contact person. This is particularly important as participants may live with both parents but only one parent is aware of the participant's gender identity. Information about interim development of personal or family risk factors of thrombosis will be obtained from the participant and, for participants under age 18 years, from the parent(s) that the participant identifies as being aware of the participant's gender identity, hormone use, and study participation. All study materials will be carefully crafted to convey the important study information while minimizing the risk of breaching the participant's confidentiality around gender identity (for example, should a parent who is unaware of the patient's gender identify discover information related to the study). Should a participant's gender identity be inadvertently disclosed, the transgender clinical team and social worker will be notified immediately, and the participant and family member will be directed to seek care in an emergency department or call 911 should they feel in danger. For families who feel unsafe or uncomfortable (but not in

immediate danger), they will be seen as soon as possible (within 24 hours, if at all possible) in the Transgender Health Clinic. The study team will also notify the IRB.

2. Emotional distress: Participants will be told at each study visit that they can opt out of any question at any time or end their participation in that study visit (or the entire study) should they become distressed. Should a participant become emotionally distressed during his/her/their study participation, the study staff will notify Dr. Tanya Mullins and the participant's transgender clinical provider(s). Study staff and clinical staff will work with the participant to identify means of resolving the distress including but not limited to connections to the social workers associated with the Transgender Health Clinic or the Division of Adolescent and Transition Medicine clinic. The study team will also notify the IRB.

3. Disclosure of suicidal ideation: Should a participant disclose suicidal ideation, study staff will notify the PI and the clinical team of the Transgender Health Team by phone or pager. Further acute management will be determined by the participant's clinical team. Participants will not be permitted to leave the study visit until a determination of further management is made by the participant's clinical team. Study visits will be scheduled to occur during regular business hours in order to ensure that adequate support is available for participants should emotional distress or disclosure of suicidal ideation occur. The study team will also notify the IRB.

4. Disclosure of new personal or family risk factors for thrombosis: Should such information be reported by the participant or parent, this information will be relayed by study staff to the participant's clinical provider within 48 hours. Further management will be determined by the clinical team. Dr. Tanya Mullins will also be notified. This plan will be included in the informed consent/assent documents.

5. Disclosure of additional hormone use not prescribed through the Transgender Health Clinic or inappropriate dosage: Because additional hormone use or use of different dosages than prescribed may impact the clinical care provided by the Transgender Health Clinic, such information will be relayed by study staff to the participant's clinical provider within 48 hours. This plan will be included in the informed consent/assent documents.

6. Abnormal study test results: All test results will be reviewed by the PI and co-I. Clinically significant abnormalities will be reported to the participant's clinical provider within 48 hours of review of results. Because estrogen-mediated platelet hyperreactivity is of unknown clinical significance and is not a clinically available test, findings from these tests will be reviewed by (b)(6) and communicated to the participant's primary transgender care provider if necessary.

7. Blood sampling: Only staff trained in phlebotomy procedures will draw blood. Adverse events will be captured and reported to the IRB. Juice and snacks are available in the Schubert Research Clinic where blood samples will be taken, in the event that a participant feels dizzy. Topical freeze spray is also available.

Vulnerable Subjects

1. Children: This study recruits adolescents under the age of 18 years. Consistent with recommendations from the CCHMC IRB, we will obtain assent from all adolescents under the age of 18 years, as well as consent from one parent for youth under the age of 18 years for additional protection.

2. Transgender and gender-nonconforming youth are considered a vulnerable population due to the socially stigmatized nature of having this gender identity. Inadvertent breach of confidentiality in which a participant's name is linked to a study recruiting people who are seeking gender-care could be particularly harmful. We believe that the protections that we plan to implement as described above (including using codes, secure data storage, attention to crafting of study documents) minimize this risk. In addition, the CRC will obtain permission from the transgender clinical provider prior to approaching the potential participant about the study.

3. Patients: Some of the potential participants receive primary care services through the Division of Adolescent and Transition Medicine and thus may have clinical visits with Dr. Tanya Mullins. Similarly, many patients may receive gender care from (b)(6) In order to minimize the risk of perceived coercion, only the study clinical research coordinator will be responsible for recruitment and consent procedures.

Potential Benefits of the Proposed Research to Research Participants and Others

This proposal most closely fits classification as minimal risk with no direct benefit to participants. Participation may benefit others as the study will improve our understanding of the prevalence of personal and family risk factors for thrombosis and whether longitudinal changes in the hemostatic system occur with ongoing use of

estrogen gender-affirming hormone therapy. This knowledge will allow clinicians to provide more complete counseling to patients and families about the risks of estrogen gender-affirming hormone therapy.

Importance of the Knowledge to be Gained

The research proposed in this aim is a critical step to understanding the risk of thrombosis for transgender adolescents and young adults using estrogen gender-affirming hormone therapy, which is necessary for clinicians, patients, and families to make informed decisions about hormone therapy. Understanding the changes that occur in the hemostatic system in response to estrogen gender-affirming hormone therapy will allow for tailored clinical approaches to youth who may be at higher risk of thrombosis due to personal and family risk factors.

DATA AND SAFETY MONITORING PLAN

Specific Aim 1: In a population of transgender women (up to age 22 years at gender-affirming hormone therapy start), prospectively determine changes in coagulation that would predispose to thrombosis over the first 24 months of estrogen gender-affirming hormone therapy.

I. Description of Potential Harms

Clinical research with transgender youth is associated with risks of breach of confidentiality and psychological distress that may be beyond that expected with other patient populations. For transgender youth, the risk of breach of confidentiality with respect to participation in the study is a recognized risk similar to that of other study participants (and addressed in the human subjects document for Aim 1). Risks and management plan for abnormal laboratory test results are also detailed in the human subjects document for Aim 1. An additional risk unique to this population is risk of breach of confidentiality by inadvertently sharing the participant's gender identity with other people (including family members or other members of their close social circle) who may not be aware of the patient's gender. Thus, while youth may present for clinic or study visits as their affirmed gender (the gender with which they identify) and using their preferred name and pronouns, youth may still be living in their birth gender or using their birth name and pronouns in other situations. Risks of inadvertent disclosure of gender identity for the participant range from psychological distress to concerns for physical safety.

II. Safety Monitoring Plan

The study team has worked closely with physicians caring for youth in the Transgender Health Clinic (including (b)(6) to develop this safety monitoring plan in order to ensure the highest level of protection possible against these risks. The steps that will be taken to minimize these risks are described in the "Human Subjects Aim 1 Thrombosis Risk in Transgender Youth" document. The clinical research coordinator and PI (Dr. Tanya Mullins) will provide ongoing monitoring of any reports of inadvertent disclosure of gender identity among participants and any reports of psychological distress during study visits (in-person or by telephone). Should Dr. Tanya Mullins not be available (i.e., out of the office), (b)(6) or another physician in the Transgender Health Clinic or Teen Health Center will serve as the contact person for any emergent issues.

II.A. Disclosure of Gender Identity: Should a participant's gender identity be inadvertently disclosed, the transgender clinical team and social worker will be notified immediately, and the participant and family member will be directed to seek care in an emergency department or call 911 should they feel in danger. For families who feel unsafe or uncomfortable (but not in immediate danger), they will be seen as soon as possible (within 24 hours, if at all possible) in the Transgender Health Clinic.

II.B. Disclosure of Psychological Distress: For participants who disclose emotional distress, they may opt out of any question at any time or end their participation in that study visit (or the entire study). Should a participant become emotionally distressed during his/her/their study participation, the study staff will notify Dr. Tanya Mullins (or the covering contact physician) and the participant's transgender clinical provider(s). Study staff and clinical staff will work with the participant to identify means of resolving the distress including but not limited to connections to the social workers associated with the Transgender Health Clinic or the Division of Adolescent and Transition Medicine clinic.

II.C. Disclosure of Suicidal Ideation: Should a participant disclose suicidal ideation, study staff will notify the PI and the clinical team of the Transgender Health Team by phone or pager. Further acute management will be determined by the participant's clinical team. Participants will not be permitted to leave the study visit until a determination of further management is made by the participant's clinical team. Study visits will be scheduled to occur during regular business hours in order to ensure that adequate support is available for participants should emotional distress or disclosure of suicidal ideation occur.

III. Reporting to IRB and NIH Institute

The study team will notify the IRB in accordance with Cincinnati Children's Hospital Medical Center (CCHMC) Research Policy R-18 and CCHMC guidance: IRB Reporting Requirements for Unanticipated Problems Related to Research (Version: 21 April 2009). As per NHLBI-specific requirements, the study team will submit an IRB-approved safety monitoring plan if the protocol is deemed greater than minimal risk and will also follow NHLBI reporting guidelines as detailed in the "NHLBI Adverse Event and Unanticipated Problem Reporting Policy."

Section 4 - Protocol Synopsis (Study 1)

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? ❍ Yes ❍ No

4.7. Dissemination Plan

Section 1 - Basic Information (Study 2)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis 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 2)

2.1. Conditions or Focus of Study

- - Health services for transgender persons
- - Attitude of health personnel
- - Anticoagulants
- - Practice patterns, physicians
- - Qualitative research
- - Transgender persons
- - Gender identity
- - Young adult
- - Thrombosis
- - Risk factors
- - Adolescent

2.2. Eligibility Criteria

Inclusion criteria:
- Hematologists who care for youth (ages 22 years and younger)
- Medical staff member at an institution that is part of the (b)(6) (Cincinnati Children's Hospital Medical Center, Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN])

Exclusion criteria:
- Unable to understand written and spoken English

2.3. Age Limits	Min Age: N/A (No limit)	Max Age: N/A (No limit)
2.3.a. Inclusion of Individuals Across the Lifespan	Inclusion_Across_Lifespan_Aim_2_Hematologists.pdf	
2.4. Inclusion of Women and Minorities	Inclusion_of_Women_and_Minorities_Aim_2.pdf	
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Aim_2_1_Interviews.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	See_Study_Timeline_2_1.pdf	
2.8. Enrollment of First Participant	10/01/2022	Anticipated

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to TG youth with personal/family risk factors that increase thrombosis risk.

Because this aim explores the attitudes and practices of hematology clinicians toward recommending thromboprophylaxis, no children will be recruited for this aim. There will be no upper or lower age limit for recruitment of hematology clinicians who otherwise meet inclusion criteria.

INCLUSION OF WOMEN AND MINORITIES

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender (TG) youth with personal/family risk factors that increase thrombosis risk.

In all phases of Aim 2, male and female physicians will be recruited. In addition, minority physicians will also be recruited. We do not anticipate targeted recruitment based on either gender or minority status, but no gender or minority will be excluded from the study. For Phases 1 and 2, we will be recruiting from among physicians practicing in Cincinnati, OH; Columbus, OH; Pittsburgh, PA; and Indianapolis, IN. Based on available data from the U.S. Census Bureau for the counties in which these cities are located, we estimate that 51.6% will be female and 48.4% male; 69.5% will be white, 23.2% Black/African American, 13.5% Asian, 0.3% American Indian/Alaska Native, and 2.8% multiracial. We estimate 5.8% of the sample will identify as Latino.[211] For Phase 3, we will be recruiting a sample of physicians from the U.S. and Canada. We will not be targeting recruitment based on gender or minority status, but no gender or minority will be excluded from the study. Based on data about U.S. physicians published by the Association of American Medical Colleges (AAMC), we expect 64.1% males and 35.9% females. From this available race/ethnicity data, we expect 65.7% white, 5.8% Black/African-American, 20% Asian, 0.35% American Indian/Alaska Native, 0.1% Native Hawaiian/Pacific Islander, and 6.8% Hispanic.[212]

RECRUITMENT AND RETENTION PLAN

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender (TG) youth with personal/family risk factors that increase thrombosis risk.

Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth

I. RECRUITMENT PLAN

Recruitment location

Regional hematologists (pediatric or adult) will be recruited from institutions that are members of the (b)(6) (b)(6), an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (Cincinnati Children's Hospital Medical Center [CCHMC], Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for transgender youth at increased risk of thrombosis or who have had thrombosis. However, the study will recruit any hematologist who provides care to adolescents or young adults 22 years of age or younger in order to capture the range of salient attitudes toward recommending thromboprophylaxis to youth at increased risk of thrombosis.

Patient characteristics and sample size

Fifteen to 20 hematologists (pediatric or adult) who care for youth (ages 22 years and younger) will be recruited from the above institutions to participate in one-time individual interviews via CCHMC IRB approved video platform (Zoom) with the PI (T. Mullins). The exclusion criterion is inability to understand English. We will plan for approximately 15-20 interviews in order to meet sample size recommendations for qualitative interview studies seeking to achieve maximum variation.[154] However, we will maintain flexibility in total number of interviews in order to reach informational redundancy. Participants will receive $100 in compensation for their time.

Sampling strategy

Participants will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (CCHMC, Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for transgender youth at increased risk of thrombosis or who have had thrombosis. Invitations to the study will be mailed electronically to the business e-mail address of potential participants every 3 weeks. If no response is received after 3 attempts, the potential participant will be removed from the recruitment list and an alternate will be contacted.

Modes of recruitment

Recruitment will be by direct e-mail communication from study staff to the business e-mail address of potential participants. Emails will include the rationale for the study, why the potential participant is being invited to participate, study procedures, study information page, and how to contact the study team to participate. Interviews will be scheduled by study staff to occur via video at a time convenient for the participant. There are at least 45-50 physicians specializing in hematology between the 4 target institutions. Thus, there are sufficient numbers of clinicians from which to recruit. In total, we estimate recruitment will take 9 months.

II. RETENTION PLAN

As there are no longitudinal components to this part of the proposed study, there are no retention activities planned.

See information for attachment “Study Timeline” in Study Record “Aim 1: Thrombosis Risk in Young Transgender Women.”

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 2, IER 1	Domestic	Academic site Hospital

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth

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): Academic site
Hospital

6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	2	0	0	4
White	7	7	0	1	15
More than One Race	0	0	0	0	0
Total	10	9	0	1	20

Cumulative (Actual)

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

Section 3 - Protection and Monitoring Plans (Study 2)

3.1. Protection of Human Subjects	Human_Subjects_Aim_2_1_Interviews.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ● No
3.5. Overall structure of the study team	

PROTECTION OF HUMAN SUBJECTS

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender youth with personal/family risk factors that increase thrombosis risk.

Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth

Risks to Human Subjects

Human Subjects Involvement and Design

For the qualitative portion of this study (Aim 2.1), we will recruit 15-20 hematologists (pediatric or adult) who care for youth (ages 22 years and younger) in the local region. Participants will be recruited from institutions that are members of the (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (Cincinnati Children's Hospital Medical Center [CCHMC], Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for transgender youth at increased risk of thrombosis or who have had thrombosis. Invitations to the study will be mailed electronically to the business e-mail address of potential participants every 3 weeks. Participants will complete one semi-structured interview by video conducted by an experienced interviewer (Dr. T. Mullins [PI]).

Characteristics

Participants will be recruited from among hematologists (pediatric or adult) from institutions that are members of the (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth. We are targeting hematologists who care for adolescents and/or young adults ages 22 years and younger as these youth are underrepresented in past research with transgender patients, and this topic is of great interest to pediatric hematologists (i.e., the work of our group was highlighted at the recent American Society of Hematology meeting, invited presentations at national meetings such as the Foundation for Women and Girls with Bleeding Disorders). Potential participants are likely to have made or will be making decisions about evaluation and management of transgender youth at risk of thrombosis, including decisions about thromboprophylaxis. We anticipate recruiting up to 20 hematologists but will maintain flexibility in order to achieve thematic saturation. Exclusion criteria: Unable to understand written and spoken English.

Study Procedures, Materials, and Potential Risks

Procedures

We will perform a cross-sectional qualitative study consisting of one-time semi-structured interviews conducted via video by the PI.

Materials

The research materials to be collected from human subjects include interview data obtained through individual semi-structured interviews, recordings of these interviews, and the transcripts resulting from these interviews. Interview content will include: demographics, practice characteristics, knowledge about transgender health, comfort communicating with transgender youth, attitudes toward transgender youth, experiences providing thromboprophylaxis to transgender youth, theory-based predictors, structural and policy factors, and intentions to recommend and prescribe thromboprophylaxis to transgender youth. Interviews will be de-identified because this is a one-time interview and no follow-up with participants is necessary.

1. Interview recording: No protected health information (PHI) is being collected during interviews. Interviews will last approximately 60 minutes and will be recorded. All interview recordings will be stored on a secure, password-protected, limited-access network drive. Only study personnel will have access to the data. Audio-only recordings will be sent for transcription (see below). Video recordings will be kept temporarily in order for study staff to add field notes to de-identified transcripts (such as non-verbal cues). All recordings will be expunged at the close of the study to minimize breach of confidentiality.

2. Interview transcripts: Audio-recordings of interviews will be transcribed by an independent, HIPAA-

compliant transcriptionist and cleaned by study staff. Transcribed interviews will be de-identified and stored on a secure, password-protected, limited-access network drive. Any hard copies of data will be kept in locked cabinets within a locked office suite. Only study personnel will have access to the data.

3. Enrollment and contact information log: In order to ensure that participants are enrolled only once and to provide incentives, a temporary list of participants' names/contact information will be kept. All information will be stored on a secure, password-protected, limited-access network drive. This will be expunged at the close of the study.

Potential Risks

We estimate that the risks of participation in this study are minimal since the participation of human subjects is limited to interviews alone. There is a small risk of breach of confidentiality because interviews will be recorded and transcribed. However, through the efforts described above, we expect that we have minimized this risk. To further minimize risks and protect participants' confidentiality, all members of the study team will have completed mandated training procedures and certifications. Potential risks include:

1. Breach of confidentiality: Because interviews will be recorded and transcribed, there is a small risk of breach of confidentiality. There is also a risk of breach of confidentiality from having the enrollment and contact information log.

2. Emotional discomfort: Some participants may be uncomfortable discussing care for transgender youth, but because all participants are experienced physicians, we expect this discomfort to be minimal.

Adequacy of Protection Against Risks

Informed Consent

Prior to initiating the study, approval from the Institutional Review Board (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) will be obtained. CCHMC will serve as the IRB of record. Invitations to the study will be mailed electronically by study staff to the business e-mail address of potential participants every 3 weeks. Interviews will be conducted by the PI. All potential participants will be informed of their right to terminate participation in the study at any time. All interviews will be via CCHMC IRB-approved video platform (i.e., Zoom) at a time convenient to the participant. We will request that participants complete interviews in a private room in order to minimize breach of confidentiality. The PI will conduct interviews from a private location (e.g., her private business office). Potential participants will not be contacted by telephone by study staff without the participant's requesting such contact. All required elements of informed consent will be delivered as a written study information sheet via e-mail and reviewed again verbally prior to conducting the interview. We will request a waiver of written consent from the IRB because a signed informed consent document would be the only record linking the subject to the research and the major risk of the study is breach of confidentiality. In addition, the study is no more than minimal risk of harm and involves interviews, which would not require written consent outside of the research setting. Participation in the interview will be deemed consent to participate.

Protections Against Risk

1. Breach of confidentiality: Recordings and transcripts of interviews will be assigned a study identification number and stored on a secure, password-protected, limited-access network drive. Therefore, no identifying information will be associated with audio-recordings or transcripts. Video recordings will be kept temporarily to allow for addition of field notes to transcripts of the audio-recordings. Video and audio recordings will be expunged at the close of the study. A temporary password-protected electronic file containing the names and contact information of participants will be maintained for the duration of the study in order to ensure that participants are enrolled only once. Transcripts will be de-identified. All paper data forms will be kept in locked cabinets, and electronic files will be stored on a secure, password-protected, limited-access network drive. Only study personnel will have access to the data. We will request a waiver of signed informed consent to further minimize the risk of inadvertent breach of confidentiality.

2. Emotional discomfort: Participants will be told at the beginning of each interview that they can opt out of any interview question at any time throughout the interview or end their participation at any time should they become uncomfortable.

Vulnerable Subjects

Pregnant women also may be involved in the study. The proposed study would also be minimal risk for pregnant women with the same potential risks as those noted above. The same protections would be applied to pregnant participants.

Potential Benefits of the Proposed Research to Research Participants and Others

This proposal most closely fits classification as minimal risk with no direct benefit to participants. Participation may benefit others as the study will improve our understanding about which transgender youth should have hematologic evaluation prior to starting gender-affirming hormone therapy and which youth might benefit from thromboprophylaxis, which will allow clinicians to provide better guidance to patients and families making decisions about gender-affirming hormone therapy.

Importance of the Knowledge to be Gained

Taken together, the research proposed in this aim is a critical step in understanding the attitudes and intended practices of hematologists toward evaluation and management of transgender youth on gender-affirming hormone therapy, including potential prescription of thromboprophylaxis. Such information is critical to developing guidance for clinicians providing gender care about which patients should be referred for further hematologic evaluation and guidance for hematologists evaluating such youth.

Section 4 - Protocol Synopsis (Study 2)

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? ❍ Yes ❍ No

4.7. Dissemination Plan

Section 1 - Basic Information (Study 3)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

Aim 2.2a: Cognitive Interviews for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis 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 3)

2.1. Conditions or Focus of Study

- - Health services for transgender persons
- - Attitude of health personnel
- - Anticoagulants
- - Practice patterns, physicians
- - Transgender persons
- - Gender identity
- - Adolescent
- - Young adult
- - Thrombosis
- - Risk factors
- - Questionnaire design

2.2. Eligibility Criteria

Inclusion criteria:
- Hematologists who care for youth (ages 22 years and younger)
- Medical staff member at an institution that is part of the (b)(6) (Cincinnati Children's Hospital Medical Center, Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN])

Exclusion criteria:
- Unable to understand written and spoken English

2.3. Age Limits	Min Age: N/A (No limit) Max Age: N/A (No limit)
2.3.a. Inclusion of Individuals Across the Lifespan	See_Inclusion_Across_Lifespan_2_2a.pdf
2.4. Inclusion of Women and Minorities	See_Inclusion_of_Women_and_Minorities_2_2a.pdf
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Aim_2_2a_Cognitive_I.pdf
2.6. Recruitment Status	Not yet recruiting
2.7. Study Timeline	See_Study_Timeline_2_2a.pdf
2.8. Enrollment of First Participant	07/01/2024 Anticipated

See information for attachment “Inclusion Across Lifespan Aim 2 Hematologists” in Study Record “Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth.”

See information for attachment “Inclusion of Women and Minorities Aim 2” in Study Record “Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth.”

RECRUITMENT AND RETENTION PLAN

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender (TG) youth with personal/family risk factors that increase thrombosis risk.

Aim 2.2a: Cognitive Interviews for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth

I. RECRUITMENT PLAN

Recruitment location

Regional hematologists will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (Cincinnati Children's Hospital Medical Center [CCHMC], Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]).

Patient characteristics and sample size

Cognitive interviewing, which is a process during which potential participants provide interpretations of the survey questions and responses, will be the first method used to ensure that the survey items are clear and understandable.[162] Consistent with recommendations for cognitive interviewing,[217] participants will include 5 hematologists (pediatric or adult) for the first round. We will maintain flexibility to conduct a second round of 5 cognitive interviews depending on the findings of the first round, with survey revision occurring between rounds.[217] Participants will receive $100 in compensation for their time.

Sampling strategy

Participants will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (CCHMC, Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for transgender youth at increased risk of thrombosis or who have had thrombosis. Invitations to the study will be mailed electronically to the business e-mail address of potential participants every 3 weeks. If no response is received after 3 attempts, the potential participant will be removed from the recruitment list and an alternate will be contacted.

Modes of recruitment

Recruitment will be by direct e-mail communication from study staff to the business e-mail address of potential participants. Emails will include the rationale for the study, why the potential participant is being invited to participate, study procedures, study information page, and how to contact the study team to participate. Cognitive interviews will be scheduled by study staff to occur via video at a time convenient for the participant. There are at least 45-50 physicians specializing in hematology between the 4 target institutions. Thus, there are sufficient numbers of patients from which to recruit. In total, we estimate recruitment will take 6 months.

II. RETENTION PLAN

As there are no longitudinal components to this part of the proposed study, there are no retention activities planned.

See information for attachment “Study Timeline” in Study Record “Aim 1: Thrombosis Risk in Young Transgender Women.”

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 3, IER 1	Domestic	Academic site Hospital

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : Aim 2.2a: Cognitive Interviews for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth

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): Academic site
Hospital

6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	1	0	0	1
White	2	2	0	0	4
More than One Race	0	0	0	0	0
Total	2	3	0	0	5

Cumulative (Actual)

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

Section 3 - Protection and Monitoring Plans (Study 3)

3.1. Protection of Human Subjects	Human_Subjects_Aim_2_2a_Cognitive_Interviews.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ● No
3.5. Overall structure of the study team	

PROTECTION OF HUMAN SUBJECTS

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender youth with personal/family risk factors that increase thrombosis risk.

Aim 2.2a: Cognitive Interviews for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth

Risks to Human Subjects

Human Subjects Involvement and Design

The findings from the individual interviews conducted in Aim 2.1 will inform the development of new survey items designed to measure the intentions of hematologists toward prescribing thromboprophylaxis to transgender youth starting gender-affirming hormone therapy, and factors influencing these intentions. We plan to recruit 5-10 regional hematologists (pediatric or adult) who care for youth (ages 22 years and younger). Participants will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (Cincinnati Children's Hospital Medical Center [CCHMC], Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for transgender youth at increased risk of thrombosis or who have had thrombosis. Invitations to the study will be mailed electronically to the business e-mail address of potential participants every 3 weeks. Participants will complete one cognitive interview by video conducted by an experienced interviewer (Dr. T. Mullins [PI]).

Characteristics

Participants will be recruited from among hematologists (pediatric or adult) from institutions that are members of the (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth. We are targeting hematologists who care for adolescents and/or young adults ages 22 years and younger as these youth are underrepresented in past research with transgender patients, and this topic is of great interest to pediatric hematologists (i.e., the work of our group was highlighted at the recent American Society of Hematology meeting, invited presentations at national meetings such as the Foundation for Women and Girls with Bleeding Disorders). Potential participants are likely to have made or will be making decisions about evaluation and management of transgender youth at risk of thrombosis, including decisions about thromboprophylaxis. We anticipate recruiting 5-10 hematologists for cognitive interviews (5 participants per round, up to two rounds). Exclusion criteria: Unable to understand written and spoken English.

Study Procedures, Materials, and Potential Risks

Procedures

Cognitive interviews will be done via CCHMC IRB-approved video modality (Zoom) in up to two rounds with 5 participants in each round, with revision of survey items occurring between rounds (if needed).[131] The PI (Dr. T. Mullins), who has had formal training in cognitive interviewing and experience with this methodology, will conduct the cognitive interviews. Participants will be asked to read and talk aloud as they interpret the questions and possible responses. Each individual question and possible responses will be reviewed with each participant. Cognitive interviews will last approximately 60 minutes and will be recorded. Audio-recordings will be transcribed by an independent HIPAA-compliant transcriptionist. Field notes will also be taken during the interview and when reviewing video recordings while cleaning transcripts. Field notes will not contain identifying information and will be added to de-identified interview transcripts.

Materials

The research materials to be collected from human subjects include cognitive interview data obtained through individual interviews and the transcripts resulting from these interviews.

1. Cognitive interview recording: All interview recordings will be stored on a secure, password-protected, limited-access network drive. Only study personnel will have access to the data. Audio-only

recordings will be sent for transcription (see below). Video recordings will be kept temporarily in order for study staff to add field notes to de-identified transcripts (such as non-verbal cues). All recordings will be expunged at the close of the study to minimize breach of confidentiality.

2. Cognitive interview transcripts: Audio-recordings of interviews will be transcribed by an independent HIPAA-compliant transcriptionist and cleaned by study staff. Transcribed interviews will be de-identified and stored on a secure, password-protected, limited-access network drive. Any hard copies of data will be kept in locked cabinets within a locked office suite. Only study personnel will have access to the data.

3. Enrollment and contact information log: In order to ensure that participants are enrolled only once and to provide incentives, a temporary list of participants' names/contact information will be kept. All information will be stored on a secure, password-protected, limited-access network drive. This will be expunged at the close of the study.

Potential Risks

We estimate that the risks of participation in this study are minimal since the participation of human subjects is limited to cognitive interviews alone, and the focus of these interviews is on survey development and not the responses of the participant to the questions. There is a small risk of breach of confidentiality because interviews will be recorded and transcribed. However, through the efforts described above, we expect that we have minimized this risk. To further minimize risks and protect participants' confidentiality, all members of the study team will have completed mandated training procedures and certifications. Potential risks include:

1. Breach of confidentiality: Because interviews will be recorded, transcribed, and field notes taken, there is a small risk of breach of confidentiality. There is also a risk of breach of confidentiality from having the enrollment and contact information log.

2. Emotional discomfort: Some participants may be uncomfortable discussing care for transgender youth, but because all participants are experienced physicians, we expect this discomfort to be minimal.

Adequacy of Protection Against Risks

Informed Consent

Prior to initiating the study, approval from the Institutional Review Board (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) will be obtained. CCHMC will serve as the IRB of record. Invitations to the study will be mailed electronically by study staff to the business e-mail address of potential participants every 3 weeks. Interviews will be conducted by the PI. All potential participants will be informed of their right to terminate participation in the study at any time. All cognitive interviews will be via CCHMC IRB-approved video platform (i.e., Zoom) at a time convenient to the participant. We will request that participants complete cognitive interviews in a private room in order to minimize breach of confidentiality. The PI will conduct interviews from a private location (e.g., her private business office). Potential participants will not be contacted by telephone by study staff without the participant's requesting such contact. All required elements of informed consent will be delivered as a written study information sheet via e-mail and reviewed again verbally prior to conducting the interview. We will request a waiver of written consent from the IRB because a signed informed consent document would be the only record linking the subject to the research and the major risk of the study is breach of confidentiality. In addition, the study is no more than minimal risk of harm and involves cognitive interviews, which would not require written consent outside of the research setting. The focus of these cognitive interviews is survey item development and not the responses of the participant to the survey items. Participation in the cognitive interview will be deemed consent to participate.

Protections Against Risk

1. Breach of confidentiality: Recordings and transcripts of cognitive interviews will be assigned a study identification number and stored on a secure, password-protected, limited-access network drive. Therefore, no identifying information will be associated with audio-recordings or transcripts. Video recordings will be kept temporarily to allow for addition of field notes to transcripts of the audio-recordings. Video and audio recordings will be expunged at the close of the study. A temporary password-protected electronic file containing the names and contact information of participants will be maintained for the duration of the study in order to ensure that participants are enrolled only once. Transcripts will be de-identified. All paper data forms will be kept in locked cabinets, and electronic files will be stored on a secure, password-protected, limited-access network drive. Only study personnel will have access to the data. We will request a waiver of signed informed consent to further minimize the risk of inadvertent breach of confidentiality.

2. Emotional discomfort: Participants will be told at the beginning of each interview that they can opt out of any interview question at any time throughout the interview or end their participation at any time should they become uncomfortable.

Vulnerable Subjects

Pregnant women also may be involved in the study. The proposed study would also be minimal risk for pregnant women with the same potential risks as those noted above. The same protections would be applied to pregnant participants.

Potential Benefits of the Proposed Research to Research Participants and Others

This proposal most closely fits classification as minimal risk with no direct benefit to participants. Participation may benefit others as the study as a whole will improve our understanding about which transgender youth should have hematologic evaluation prior to starting gender-affirming hormone therapy and which youth may benefit from thromboprophylaxis, which will allow clinicians to provide better guidance to patients and families making decisions about gender-affirming hormone therapy.

Importance of the Knowledge to be Gained

Taken together, the research proposed in this aim is a critical step in understanding the attitudes and intended practices of hematologists toward evaluation and management of transgender youth on gender-affirming hormone therapy, including potential prescription of thromboprophylaxis. Such information is critical to developing guidance for clinicians providing gender care about which patients should be referred for further hematologic evaluation and guidance for hematologists who evaluate such youth.

Section 4 - Protocol Synopsis (Study 3)

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? ❍ Yes ❍ No

4.7. Dissemination Plan

Section 1 - Basic Information (Study 4)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

Aim 2.2b: Pilot Testing for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis 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 4)

2.1. Conditions or Focus of Study

- - Health services for transgender persons
- - Attitude of health personnel
- - Anticoagulants
- - Practice patterns, physicians
- - Transgender persons
- - Gender identity
- - Adolescent
- - Young adult
- - Thrombosis
- - Risk factors
- - Questionnaire design

2.2. Eligibility Criteria

Inclusion criteria:
- Hematologists who care for youth (ages 22 years and younger)
- Medical staff member at an institution that is part of the (b)(6) (Cincinnati Children's Hospital Medical Center, Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN])

Exclusion criteria:
- Unable to understand written and spoken English

2.3. Age Limits	Min Age: N/A (No limit) Max Age: N/A (No limit)
2.3.a. Inclusion of Individuals Across the Lifespan	See_Inclusion_Across_Lifespan_2_2b.pdf
2.4. Inclusion of Women and Minorities	See_Inclusion_of_Women_and_Minorities_2_2b.pdf
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Aim_2_2b_Pilot_Testi.pdf
2.6. Recruitment Status	Not yet recruiting
2.7. Study Timeline	See_Study_Timeline_2_2b.pdf
2.8. Enrollment of First Participant	04/01/2025 Anticipated

See information for attachment “Inclusion Across Lifespan Aim 2 Hematologists” in Study Record “Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth.”

See information for attachment “Inclusion of Women and Minorities Aim 2” in Study Record “Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth.”

RECRUITMENT AND RETENTION PLAN

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender (TG) youth with personal/family risk factors that increase thrombosis risk.

Aim 2.2b: Pilot Testing for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth

I. RECRUITMENT PLAN

Recruitment location

Regional hematologists (pediatric or adult) will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (Cincinnati Children's Hospital Medical Center [CCHMC], Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]).

Patient characteristics and sample size

Participants in pilot testing will provide comments regarding question clarity, in addition to providing preliminary data about the performance of items as detailed in "Approach." Consistent with recommendations for pilot testing,[163] pilot testing will be done with 5-10 hematologists, although we will maintain flexibility to expand recruitment if necessary. Participants in pilot testing will receive $50 in compensation for their time.

Sampling strategy

Participants will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (CCHMC, Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for transgender youth at increased risk of thrombosis or who have had thrombosis. Invitations to the study will be mailed electronically to the business e-mail address of potential participants every 3 weeks. If no response is received after 3 attempts, the potential participant will be removed from the recruitment list and an alternate will be contacted.

Modes of recruitment

Recruitment will be by direct e-mail communication from study staff to the business e-mail address of potential participants. Emails will include the rationale for the study, why the potential participant is being invited to participate, study procedures, study information page, and how to contact the study team to participate. Pilot testing will be scheduled by study staff to occur via video at a time convenient for the participant. There are at least 45-50 physicians specializing in hematology between the 4 target institutions. Thus, there are sufficient numbers of patients from which to recruit. In total, we estimate recruitment will take 6-9 months.

II. RETENTION PLAN

As there are no longitudinal components to this part of the proposed study, there are no retention activities planned.

See information for attachment “Study Timeline” in Study Record “Aim 1: Thrombosis Risk in Young Transgender Women.”

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 4, IER 1	Domestic	Academic site Hospital

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : Aim 2.2b: Pilot Testing for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth

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): Academic site
Hospital

6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	0	2
White	4	3	0	1	8
More than One Race	0	0	0	0	0
Total	5	4	0	1	10

Cumulative (Actual)

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

Section 3 - Protection and Monitoring Plans (Study 4)

3.1. Protection of Human Subjects	Human_Subjects_Aim_2_2b_Pilot_Testing.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ● No
3.5. Overall structure of the study team	

PROTECTION OF HUMAN SUBJECTS

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender youth with personal/family risk factors that increase thrombosis risk.

Aim 2.2b: Pilot Testing for Developing Survey Items to Assess Hematologists' Attitudes toward Thromboprophylaxis in Transgender Youth

Risks to Human Subjects

Human Subjects Involvement and Design

Pilot testing of the survey items will be performed following refinement through cognitive interviewing. We plan to recruit 5-10 regional hematologists (pediatric or adult) who care for youth (ages 22 years and younger). Participants will be recruited from institutions that are members of the (b)(6) (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing transgender care to youth (Cincinnati Children's Hospital Medical Center [CCHMC], Children's Hospital of Pittsburgh, Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN]). This will ensure recruitment of hematologists who are likely to have cared for transgender youth at increased risk of thrombosis or who have had thrombosis. Invitations to the study will be mailed electronically to the business e-mail address of potential participants every 3 weeks. Participants will complete one pilot test by video conducted by an experienced researcher (Dr. T. Mullins [PI]).

Characteristics

Participants will be recruited from among hematologists (pediatric or adult) from institutions that are members of the (b)(6) an established relationship between several large academic institutions in the midwestern U.S. which each have dedicated clinics providing TG care to youth. We are targeting hematologists who care for adolescents and/or young adults ages 22 years and younger as these youth are underrepresented in past research with transgender patients, and this topic is of great interest to pediatric hematologists (i.e., the work of our group was highlighted at the recent American Society of Hematology meeting, invited presentations at national meetings such as the Foundation for Women and Girls with Bleeding Disorders). Potential participants are likely to have made or will be making decisions about evaluation and management of transgender youth at risk of thrombosis, including decisions about thromboprophylaxis. We anticipate recruiting 5-10 hematologists for pilot testing. Exclusion criteria: Unable to understand written and spoken English.

Study Procedures, Materials, and Potential Risks

Procedures

Pilot tests will be administered by the PI (Dr. T. Mullins) in a face-to-face meeting via CCHMC IRB-approved video platform (Zoom). Because the final survey will be administered electronically, pilot tests also will be administered electronically using Research Electronic Data Capture (REDCap) software. Video meetings for pilot test completion will allow participants in pilot testing opportunities to provide comments regarding question clarity. Field notes on questions will be taken, but no recordings will be done.

Materials

The research materials to be collected from human subjects include pilot test responses and comments regarding the survey items. Because this is a one-time pilot test with no follow-up, pilot test responses will be de-identified. Codes will be used on all responses.

1. Survey responses: No protected health information (PHI) is being collected. Surveys will be coded; thus, there will be no link to identifiable information. Pilot test surveys are expected to take 20-25 minutes to complete. The data from the electronically completed pilot surveys is entered directly into the REDCap survey database by participants. Databases will be kept on a secure, password-protected, limited-access network drive. Only study personnel will have access to the data.

2. Verbal comments: The PI conducting the pilot testing will record comments that participants offer about the survey items on the pilot test. These will be transcribed into an electronic document (and linked to the survey by code only) and stored on a secure, password-protected, limited-access network drive. Only study personnel will have access to the data.

3. Enrollment and contact information log: In order to ensure that participants are enrolled only once and to provide incentives, a temporary list of participants' names/contact information will be kept. All information will be stored on a secure, password-protected, limited-access network drive. This will be expunged at the close of the study.

Potential Risks

We estimate that the risks of participation in this study are minimal, since the participation of human subjects is limited to pilot testing of survey items. No identifying information is being collected that would serve to link a participant to the pilot test responses. To further minimize risks and protect participants' confidentiality, all members of the study team will have completed mandated training procedures and certifications. Potential risks include:

1. Breach of confidentiality: There is a small risk of inadvertent breach of confidentiality. There is also a risk of breach of confidentiality from having the enrollment and contact information log.

2. Emotional discomfort: Some participants may be uncomfortable discussing care for transgender youth, but because all participants are experienced physicians, we expect this discomfort to be minimal.

Adequacy of Protection Against Risks

Informed Consent

Prior to initiating the study, approval from the Institutional Review Board (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) will be obtained. CCHMC will serve as the IRB of record. Invitations to the study will be mailed electronically by study staff to the business e-mail address of potential participants every 3 weeks. Interviews will be conducted by the PI. All potential participants will be informed of their right to terminate participation in the study at any time. All pilot tests will be via CCHMC IRB-approved video platform (i.e., Zoom) at a time convenient to the participant. We will request that participants complete pilot tests in a private room in order to minimize breach of confidentiality. The PI will conduct pilot testing from a private location (e.g., her private business office). Potential participants will not be contacted by telephone by study staff without the participant's requesting such contact. All required elements of informed consent will be delivered as a written study information sheet via e-mail and reviewed again verbally prior to conducting the interview. We will request a waiver of written consent from the IRB because a signed informed consent document would be the only record linking the subject to the research and the major risk of the study is breach of confidentiality. In addition, the study is no more than minimal risk of harm and involves pilot testing, which would not require written consent outside of the research setting. Participation in pilot testing will be deemed consent to participate.

Protections Against Risk

1. Breach of confidentiality: Electronic surveys will be administered using REDCap, which is a HIPAA-compliant online software program used by many academic research institutions. Data are password protected and only accessible to study personnel. All pilot surveys will be de-identified and contain only a code. Only study personnel will have access to the data. A temporary password-protected electronic file containing the names of participants and contact information will be maintained for the duration of the pilot test study in order to ensure that participants are enrolled only once and to provide incentives to participants. This file will be expunged at the close of the study. We will request a waiver of signed informed consent in order to further minimize the risk of inadvertent breach of confidentiality.

2. Emotional discomfort: Participants will be told at the beginning of the pilot test that they can opt out of any survey question or end their participation at any time should they become uncomfortable.

Vulnerable Subjects

Pregnant women also may be involved in the study. The proposed study would also be minimal risk for pregnant women with the same potential risks as those noted above. The same protections would be applied to pregnant participants.

Potential Benefits of the Proposed Research to Research Participants and Others

This proposal most closely fits classification as minimal risk with no direct benefit to participants. Participation may benefit others as the study as a whole will improve our understanding about which transgender youth should have hematologic evaluation prior to starting gender-affirming hormone therapy and which youth might

benefit from thromboprophylaxis, which will allow clinicians to provide better guidance to patients and families making decisions about gender-affirming hormone therapy.

Importance of the Knowledge to be Gained

Taken together, the research proposed in this aim is a critical step in understanding the attitudes and intended practices of hematologists toward evaluation and management of transgender youth on gender-affirming hormone therapy, including potential prescription of thromboprophylaxis. Such information is critical to developing guidance for clinicians providing gender care about which patients should be referred for further hematologic evaluation and guidance for hematologists who evaluate such youth.

Section 4 - Protocol Synopsis (Study 4)

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? ❍ Yes ❍ No

4.7. Dissemination Plan

Section 1 - Basic Information (Study 5)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

Aim 2.3: Survey of Hematologists to Assess Attitudes toward Thromboprophylaxis 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 5)

2.1. Conditions or Focus of Study

- - Health services for transgender persons
- - Attitude of health personnel
- - Anticoagulants
- - Practice patterns, physicians
- - Transgender persons
- - Gender identity
- - Adolescent
- - Thrombosis
- - Risk factors
- - Survey methodology
- - Young adult

2.2. Eligibility Criteria

Inclusion criteria:
- Hematologist practicing in U.S. or Canada
- Provide hematologic care to adolescents and/or young adults (any patients ages 13-22).

Exclusion criteria:
- Unable to understand written English

2.3. Age Limits	Min Age:	N/A (No limit)	Max Age:	N/A (No limit)
2.3.a. Inclusion of Individuals Across the Lifespan	See_Inclusion_Across_Lifespan_2_3.pdf			
2.4. Inclusion of Women and Minorities	See_Inclusion_of_Women_and_Minorities_2_3.pdf			
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Aim_2_3_Survey.pdf			
2.6. Recruitment Status	Not yet recruiting			
2.7. Study Timeline	See_Study_Timeline_2_3.pdf			
2.8. Enrollment of First Participant	10/01/2025	Anticipated		

See information for attachment “Inclusion Across Lifespan Aim 2 Hematologists” in Study Record “Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth.”

See information for attachment “Inclusion of Women and Minorities Aim 2” in Study Record “Aim 2.1: Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth.”

RECRUITMENT AND RETENTION PLAN

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender (TG) youth with personal/family risk factors that increase thrombosis risk.

Aim 2.3: Survey of Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth

I. RECRUITMENT PLAN

Recruitment location

A sample of U.S. and Canadian hematologists (pediatric and adult) will be recruited through the Hemostasis and Thrombosis Research Society (HTRS) and the American Society of Pediatric Hematology/Oncology (ASPHO). HTRS is a professional society for North American health care professionals with interests in hemostatic and thrombotic disorders. In 2020, HTRS had 261 core doctoral-level faculty members and 171 trainee members (who transition to core membership following completion of fellowship). ASPHO is a multidisciplinary organization whose members care for children and youth with blood disorders and cancer, and 61% of members are pediatric hematologists or hematologists/oncologists (n=1220).

Patient characteristics and sample size

Eligible participants include physicians practicing hematology in the U.S. or Canada who provide hematologic care to adolescents and/or young adults (any patients aged 13-22 years). Potential participants who are unable to understand written English will be excluded. Based on our power calculations, we will contact 370 potential participants in order to obtain 133 completed surveys, assuming that 80% of potential participants meet eligibility criteria and a 45% response rate. Surveys administered through similar subspecialty networks, including one of our proposed networks, have achieved response rates of 29-47% (without reported incentives).[128,184,185] To maximize our response rate, we will maximize brevity of the survey and provide a monetary incentive.[170,194] Studies suggest that a smaller incentive is the most cost-effective way to maximize responses to physician surveys,[195,196] and a promised incentive increases the response rate (as opposed to lotteries).[163,197] Participants will receive $20 mailed gift card in compensation for their time.

Sampling strategy

Recruitment through the HTRS and ASPHO professional societies will allow targeted recruitment of clinicians with interests in hemostatic and thrombotic disorders and hematologic care of youth. Thus, the topical relevance of the survey to these potential participants is high, which should improve survey participation. Surveys will be completed online, following established methods to maximize survey completion.[169,170] Emails including a cover letter detailing the purpose of the survey and the survey link will be sent to the business email address of HTRS members from the society directly as per their standard practice. Similar emails will be sent by the research team to ASPHO members. A reminder email with the survey link will be sent 2-3 weeks later, with a third reminder 2-3 weeks thereafter.[171]

Modes of recruitment

Mode of recruitment will be direct emails to potential participants that will be sent by the professional society for HTRS members and by the research team for ASPHO members. Email recruitment messages sent directly from the professional society have the advantage of being more likely to be opened and/or completed, as well as being less likely to be flagged as high-risk e-mail by workplace servers. Based on current membership statistics above, we expect that there will be sufficient numbers of professionals to approach for completion of the survey. Should we not achieve our goal number of completed surveys through HTRS and ASPHO, we plan to recruit through other professional societies (for example, American Medical Association database lists that are for purchase, etc.) We expect survey administration to be completed within 6 months.

II. RETENTION PLAN

As there are no longitudinal components to the proposed study, there are no retention activities planned.

See information for attachment “Study Timeline” in Study Record “Aim 1: Thrombosis Risk in Young Transgender Women.”

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 5, IER 1	Domestic	Academic site Hospital

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : Aim 2.3: Survey of Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth

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): Academic site
Hospital

6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	1	0	0	1
Asian	10	17	0	0	27
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	5	0	1	9
White	31	55	3	5	94
More than One Race	1	1	0	0	2
Total	45	79	3	6	133

Cumulative (Actual)

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

Section 3 - Protection and Monitoring Plans (Study 5)

3.1. Protection of Human Subjects	Human_Subjects_Aim_2_3_Survey.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ● No
3.5. Overall structure of the study team	

PROTECTION OF HUMAN SUBJECTS

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender youth with personal/family risk factors that increase thrombosis risk.

Aim 2.3: Survey of Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender Youth

Risks to Human Subjects

Human Subjects Involvement and Design

Hematologists in the U.S. and Canada who care for youth (ages 22 years and younger) will be recruited through the Hemostasis and Thrombosis Research Society (HTRS) and the American Society of Pediatric Hematology/Oncology (ASPHO). HTRS is a professional society for North American health care professionals with interests in hemostatic and thrombotic disorders, and ASPHO is a multidisciplinary organization whose members care for children and youth with blood disorders and cancer. Surveys will be disseminated by HTRS for HTRS members and by the research team for ASPHO members. Based on our power calculations detailed in "Approach," we are targeting 133 completed surveys (and thus plan to distribute surveys to 370 potential participants).

Characteristics

A sample of U.S. and Canadian hematologists (pediatric and adult) will be recruited through the Hemostasis and Thrombosis Research Society (HTRS) and the American Society of Pediatric Hematology/Oncology (ASPHO). HTRS is a professional society for North American health care professionals with interests in hemostatic and thrombotic disorders. In 2020, HTRS had 261 core doctoral-level faculty members and 171 trainee members (who transition to core membership following completion of fellowship). ASPHO is a multidisciplinary organization whose members care for children and youth with blood disorders and cancer, and 61% of members are pediatric hematologists or hematologists/oncologists (n=1220). Inclusion criteria include physicians practicing hematology (pediatric or adult) in the U.S. or Canada, ability to understand written English, and providing hematologic care to adolescents and/or young adults (any patients age 13-22 years).

Study Procedures, Materials, and Potential Risks

Procedures

Links to the survey will be electronically sent by HTRS for HTRS member recruitment, as per the established procedures of that society. Links to surveys will be electronically sent by the study team for ASPHO members. Surveys will be administered using Research Electronic Data Capture (REDCap) software. Email invitations to participate in the study will detail the purpose of the study and include the required elements of informed consent. Due to the requirements for distribution of surveys to members by HTRS, surveys will be anonymous for all participants. Participants will be asked to provide contact information to receive the study incentive in the mail; this information will not be linked to survey responses and will be expunged at the close of the study.

Materials

Research materials to be collected from human subjects include survey responses. Surveys themselves will be de-identified.

1. Survey responses: No protected health information (PHI) is being collected. Surveys will be coded; thus, there will be no link to identifiable information. Surveys are expected to take 20-25 minutes to complete. The data from the electronically completed surveys is entered directly into the REDCap survey database by participants. Databases will be kept on a secure, password-protected, limited-access network drive. Only study personnel will have access to the data.

2. Contact information log: In order to provide incentives, a temporary list of participants' names/contact information will be kept. This information will not be linked to survey responses. All information will be stored on a secure, password-protected, limited-access network drive. This will be expunged at the close of the study.

Potential Risks

We estimate that the risks of participation in this study are minimal, since the participation of human subjects is

limited to participation in an anonymous survey. No identifying information is being collected that would serve to link a participant to survey responses. To further minimize risks and protect participants' confidentiality, all members of the study team will have completed mandated training procedures and certifications. Potential risks include:

1. Breach of confidentiality: There is a small risk of inadvertent breach of confidentiality. There is also a risk of breach of confidentiality from having the contact information log.

Adequacy of Protection Against Risks

Informed Consent

Prior to initiating the study, approval from the Institutional Review Board (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) will be obtained. CCHMC will serve as the IRB of record. Invitations to the study will be mailed electronically by HTRS (for HTRS members) or the study team (for ASPHO members) to the business e-mail address of potential participants every 2-3 weeks for a total of 3 mailings. We will request a waiver of written consent from the IRB because a signed informed consent document would be the only record linking the subject to the research and the major risk of the study is breach of confidentiality. In addition, the study is no more than minimal risk of harm and involves completion of a survey. All required elements of informed consent will be delivered as a written study information in the body of the invitation email and again on the first page of the electronic survey. We will advise participants that their completion of the survey will be considered implicit consent to participate in the study. We will provide contact information for the PI and study research coordinator for any participants who wish to discuss their participation in the study.

Protections Against Risk

1. Breach of confidentiality: Electronic surveys will be administered using REDCap, which is a HIPAA-compliant online software program used by many academic research institutions. Data are password protected and only accessible to study personnel. All surveys will be anonymous. Only study personnel will have access to the data. A temporary password-protected electronic file containing the names and addresses of participants will be maintained in order to provide incentives. This file will be expunged at the close of the study. We will request a waiver of signed informed consent in order to further minimize the risk of inadvertent breach of confidentiality.

Vulnerable Subjects

Pregnant women also may be involved in the study. The proposed study would also be minimal risk for pregnant women with the same potential risks as those noted above. The same protections would be applied to pregnant participants.

Potential Benefits of the Proposed Research to Research Participants and Others

This proposal most closely fits classification as minimal risk with no direct benefit to participants. Participation may benefit others as the study as a whole will improve our understanding about which transgender youth should have hematologic evaluation prior to starting gender-affirming hormone therapy and which youth may benefit from thromboprophylaxis, which will allow clinicians to provide better guidance to patients and families making decisions about gender-affirming hormone therapy.

Importance of the Knowledge to be Gained

Taken together, the research proposed in this aim is a critical step in understanding the attitudes and intended practices of hematologists toward evaluation and management of transgender youth on gender-affirming hormone therapy, including potential prescription of thromboprophylaxis. Such information is critical to developing guidance for clinicians providing gender care about which patients should be referred for further hematologic evaluation and guidance for hematologists who evaluate such youth.

Section 4 - Protocol Synopsis (Study 5)

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? ❍ Yes ❍ No

4.7. Dissemination Plan

Delayed Onset Studies

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

REFERENCES CITED

1. Herman JL, Flores AR, Brown TNT, Wilson BDM, Conron KJ. Age of individuals who identify as transgender in the United States. The Williams Insitute, University of California Los Angeles School of Law 2017. Available online at Age-Trans-Individuals-Jan-2017.pdf (ucla.edu). Accessed on 10/24/21.
2. Leinung MC, Joseph J. Changing demographics in transgender individuals seeking hormonal therapy: Are trans women more common than trans men? Transgend Health 2020;5(4):241-245. DOI: 10.1089/trgh.2019.0070.
3. Goodman M, Adams N, Corneil T, Kreukels B, Motmans J, Coleman E. Size and Distribution of Transgender and Gender Nonconforming Populations: A Narrative Review. Endocrinol Metab Clin North Am 2019;48(2):303-321. DOI: 10.1016/j.ecl.2019.01.001.
4. Canner JK, Harfouch O, Kodadek LM, et al. Temporal trends in gender-affirming surgery among transgender patients in the United States. JAMA Surg 2018;153(7):609-616. DOI: 10.1001/jamasurg.2017.6231.
5. Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in prevalence, treatment, and regrets. J Sex Med 2018;15(4):582-590. DOI: 10.1016/j.jsxm.2018.01.016.
6. Mullins ES, Geer R, Metcalf M, et al. Thrombosis risk in transgender adolescents receiving gender-affirming hormone therapy. Pediatrics 2021;147(4): e2020023549. DOI: 10.1542/peds.2020-023549. PMID: 33753543.
7. McFarland W, Wesson P, Turner C, et al. High HIV incidence among young and racial/ethnic minority transgender women in San Francisco: Results of a longitudinal cohort study. J Acquir Immune Defic Syndr 2020;84(1):e7-e10. DOI: 10.1097/QAI.0000000000002315.
8. Mustanski B, Liu RT. A longitudinal study of predictors of suicide attempts among lesbian, gay, bisexual, and transgender youth. Arch Sex Behav 2013;42(3):437-48. DOI: 10.1007/s10508-012-0013-9.
9. Flores AR, Herman JL, Gates GJ, Brown TNT. How many adults identify as transgender in the United States? The Williams Institute, 1`University of California Los Angeles School of Law 2017. Available online at http://williamsinstitute.law.ucla.edu/wp-content/uploads/How-Many-Adults-Identify-as-Transgender-in-the-United-States.pdf. Accessed on 10/24/21.
10. Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students - 19 states and large urban school districts, 2017. MMWR Morbidity and mortality weekly report 2019;68(3):67-71. DOI: 10.15585/mmwr.mm6803a3.
11. Eisenberg ME, Gower AL, McMorris BJ, Rider GN, Shea G, Coleman E. Risk and protective factors in the lives of transgender/gender nonconforming adolescents. J Adolesc Health 2017;61(4):521-526. DOI: 10.1016/j.jadohealth.2017.04.014.
12. James SE, Herman JL, Rankin S, Keisling M, Mottet L, Anofi M. The Report of the 2015 U.S. Transgender Survey. National Center for Transgender Equality, ed. Washington, D.C.2016.
13. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, Version 7. Int J Transgenderism 2012;13(4):165-232. DOI: 10.1080/15532739.2011.700873.
14. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017;102(11):3869-3903. DOI: 10.1210/jc.2017-01658.
15. Bauer GR, Scheim AI, Pyne J, Travers R, Hammond R. Intervenable factors associated with suicide risk in transgender persons: a respondent driven sampling study in Ontario, Canada. BMC Public Health 2015;15:525. DOI: 10.1186/s12889-015-1867-2.
16. Tucker RP, Testa RJ, Simpson TL, Shipherd JC, Blosnich JR, Lehavot K. Hormone therapy, gender affirmation surgery, and their association with recent suicidal ideation and depression symptoms in transgender veterans. Psychol Med 2018;48(14):2329-2336. DOI: 10.1017/S0033291717003853.
17. Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. Int J Pediatr Endocrinol 2020;2020:8. DOI: 10.1186/s13633-020-00078-2.

18. Roach RE, Lijfering WM, Helmerhorst FM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. J Thromb Haemost 2013;11(1):124-31. DOI: 10.1111/jth.12060.
19. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921. DOI: 10.1136/bmj.b2921.
20. Vandenbroucke JP, Rosing J, Bloemenkamp KW, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001;344(20):1527-35. DOI: 10.1056/NEJM200105173442007.
21. Johnson JV, Lowell J, Badger GJ, Rosing J, Tchaikovski S, Cushman M. Effects of oral and transdermal hormonal contraception on vascular risk markers: a randomized controlled trial. Obstet Gynecol 2008;111(2 Pt 1):278-84. DOI: 10.1097/AOG.0b013e3181626d1b.
22. Westhoff CL, Pike MC, Cremers S, Eisenberger A, Thomassen S, Rosing J. Endogenous thrombin potential changes during the first cycle of oral contraceptive use. Contraception 2017;95(5):456-463. DOI: 10.1016/j.contraception.2017.01.001.
23. Blondon M, van Hylckama Vlieg A, Wiggins KL, et al. Differential associations of oral estradiol and conjugated equine estrogen with hemostatic biomarkers. J Thromb Haemost 2014;12(6):879-86. DOI: 10.1111/jth.12560.
24. Hoibraaten E, Mowinckel MC, de Ronde H, Bertina RM, Sandset PM. Hormone replacement therapy and acquired resistance to activated protein C: results of a randomized, double-blind, placebo-controlled trial. Br J Haematol 2001;115(2):415-20. DOI: 10.1046/j.1365-2141.2001.03111.x.
25. Getahun D, Nash R, Flanders WD, et al. Cross-sex hormones and acute cardiovascular events in transgender persons. Annals of Internal Medicine 2018;169(4). DOI: 10.7326/m17-2785.
26. Wierckx K, Elaut E, Declercq E, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. Eur J Endocrinol 2013;169(4):471-8. DOI: 10.1530/EJE-13-0493.
27. Mullins TL, Lally M, Zimet G, Kahn JA, and the Adolescent Medicine Trials Network for HIV/AIDS Interventions. Clinician attitudes toward CDC interim pre-exposure prophylaxis (PrEP) guidance and operationalizing PrEP for adolescents. AIDS Patient Care STDS 2015;29(4):193-203. DOI: 10.1089/apc.2014.0273. PMCID: PMC4378662.
28. Mullins TL, Zimet G, Lally M, Kahn JA. Adolescent human immunodeficiency virus care providers' attitudes toward the use of oral pre-exposure prophylaxis in youth. AIDS Patient Care STDS 2016;30(7):339-48. DOI: 10.1089/apc.2016.0048. PMCID: PMC4948218.
29. Shaw MA, Kombrinck KW, McElhinney KE, et al. Limiting prothrombin activation to meizothrombin is compatible with survival but significantly alters hemostasis in mice. Blood 2016;128(5):721-31. DOI: 10.1182/blood-2015-11-680280. PMCID: PMC4974202.
30. Mullins ES, Stasyshyn O, Alvarez-Roman MT, et al. Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A. Haemophilia 2017;23(2):238-246. DOI: 10.1111/hae.13119. PMID: 27891721.
31. Mullins TLK, Idoine CR, Zimet GD, Kahn JA. Primary care physician attitudes and intentions toward the use of HIV pre-exposure prophylaxis in adolescents in one metropolitan region. J Adolesc Health 2019;64(5):581-588. DOI: 10.1016/j.jadohealth.2018.10.300. PMCID: PMC6478546.
32. Mullins TLK, Zimet G, Lally M, Xu J, Thornton S, Kahn JA. HIV care providers' intentions to prescribe and actual prescription of pre-exposure prophylaxis to at-risk adolescents and adults. AIDS Patient Care STDS 2017;31(12):504-516. DOI: 10.1089/apc.2017.0147. PMCID: PMC5724583.
33. de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014;134(4):696-704. DOI: 10.1542/peds.2013-2958.
34. Abou-Ismail MY, Citla Sridhar D, Nayak L. Estrogen and thrombosis: A bench to bedside review. Thromb Res 2020;192:40-51. DOI: 10.1016/j.thromres.2020.05.008.
35. Rabbani LE, Seminario NA, Sciacca RR, Chen HJ, Giardina EG. Oral conjugated equine estrogen increases plasma von Willebrand factor in postmenopausal women. J Am Coll Cardiol 2002;40(11):1991-9. DOI: 10.1016/s0735-1097(02)02565-2.
36. Harrison RL, McKee PA. Estrogen stimulates von Willebrand factor production by cultured endothelial cells. Blood 1984;63(3):657-64. (https://www.ncbi.nlm.nih.gov/pubmed/6607757).

37. Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. Circulation 1999;100(7):717-22. DOI: 10.1161/01.cir.100.7.717.
38. Middeldorp S, Meijers JC, van den Ende AE, et al. Effects on coagulation of levonorgestrel- and desogestrel-containing low dose oral contraceptives: a cross-over study. Thromb Haemost 2000;84(1):4-8. (https://www.ncbi.nlm.nih.gov/pubmed/10928461).
39. Arroyo A, Salloum-Asfar S, Perez-Sanchez C, et al. Regulation of TFPIalpha expression by miR-27a/b-3p in human endothelial cells under normal conditions and in response to androgens. Sci Rep 2017;7:43500. DOI: 10.1038/srep43500.
40. Dykes AC, Walker ID, McMahon AD, Islam SI, Tait RC. A study of Protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. Br J Haematol 2001;113(3):636-41. DOI: 10.1046/j.1365-2141.2001.02813.x.
41. Tans G, Curvers J, Middeldorp S, et al. A randomized cross-over study on the effects of levonorgestrel- and desogestrel-containing oral contraceptives on the anticoagulant pathways. Thromb Haemost 2000;84(1):15-21. (https://www.ncbi.nlm.nih.gov/pubmed/10928463).
42. Harris GM, Stendt CL, Vollenhoven BJ, Gan TE, Tipping PG. Decreased plasma tissue factor pathway inhibitor in women taking combined oral contraceptives. Am J Hematol 1999;60(3):175-80. DOI: 10.1002/(sici)1096-8652(199903)60:3<175::aid-ajh1>3.0.co;2-x.
43. Bladbjerg EM, Skouby SO, Andersen LF, Jespersen J. Effects of different progestin regimens in hormone replacement therapy on blood coagulation factor VII and tissue factor pathway inhibitor. Hum Reprod 2002;17(12):3235-41. DOI: 10.1093/humrep/17.12.3235.
44. Peverill RE, Teede HJ, Smolich JJ, et al. Effects of combined oral hormone replacement therapy on tissue factor pathway inhibitor and factor VII. Clin Sci (Lond) 2001;101(1):93-9. (https://www.ncbi.nlm.nih.gov/pubmed/11410120).
45. Hoibraaten E, Qvigstad E, Andersen TO, Mowinckel MC, Sandset PM. The effects of hormone replacement therapy (HRT) on hemostatic variables in women with previous venous thromboembolism--results from a randomized, double-blind, clinical trial. Thromb Haemost 2001;85(5):775-81. (https://www.ncbi.nlm.nih.gov/pubmed/11372667).
46. Scheres LJJ, Selier NLD, Nota NM, van Diemen JJK, Cannegieter SC, den Heijer M. Effect of gender-affirming hormone use on coagulation profiles in transmen and transwomen. J Thromb Haemost 2021;19(4):1029-1037. DOI: 10.1111/jth.15256.
47. Melissari E, Kakkar VV. The effects of oestrogen administration on the plasma free protein S and C4b-binding protein. Thromb Res 1988;49(5):489-95. DOI: 10.1016/s0049-3848(98)90006-8.
48. Cosman F, Baz-Hecht M, Cushman M, et al. Short-term effects of estrogen, tamoxifen and raloxifene on hemostasis: a randomized-controlled study and review of the literature. Thromb Res 2005;116(1):1-13. DOI: 10.1016/j.thromres.2004.09.014.
49. Bagot CN, Leishman E, Onyiaodike CC, Jordan F, Gibson VB, Freeman DJ. Changes in laboratory markers of thrombotic risk early in the first trimester of pregnancy may be linked to an increase in estradiol and progesterone. Thromb Res 2019;178:47-53. DOI: 10.1016/j.thromres.2019.03.015.
50. Lim HY, Leemaqz SY, Torkamani N, et al. Global coagulation assays in transgender women on oral and transdermal estradiol therapy. J Clin Endocrinol Metab 2020;105(7). DOI: 10.1210/clinem/dgaa262.
51. Soo Kim B, Auerbach DS, Sadhra H, et al. Sex-specific platelet activation through protease-activated Receptors reverses in myocardial infarction. Arterioscler Thromb Vasc Biol 2021;41(1):390-400. DOI: 10.1161/ATVBAHA.120.315033.
52. Rosenblum WI, el-Sabban F, Allen AD, Nelson GH, Bhatnagar AS, Choi SC. Effects of estradiol on platelet aggregation in cerebral microvessels of mice. Stroke 1985;16(6):980-4. DOI: 10.1161/01.str.16.6.980.
53. Rosenblum WI, el-Sabban F, Allen AD, Nelson GH, Bhatnagar AS, Choi S. Effects of estradiol on platelet aggregation in mouse mesenteric arterioles and ex vivo. Thromb Res 1985;39(3):253-62. DOI: 10.1016/0049-3848(85)90220-8.
54. Freudenberger T, Oppermann M, Marzoll A, et al. Differential effects of medroxyprogesterone acetate on thrombosis and atherosclerosis in mice. Br J Pharmacol 2009;158(8):1951-60. DOI: 10.1111/j.1476-5381.2009.00470.x.
55. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. Arch Sex Behav 1989;18(1):49-57. DOI: 10.1007/bf01579291.

56. Skiba MA, Bell RJ, Islam RM, Handelsman DJ, Desai R, Davis SR. Androgens during the reproductive years: What is normal for women? J Clin Endocrinol Metab 2019;104(11):5382-5392. DOI: 10.1210/jc.2019-01357.
57. Appel IM, Grimminck B, Geerts J, Stigter R, Cnossen MH, Beishuizen A. Age dependency of coagulation parameters during childhood and puberty. J Thromb Haemost 2012;10(11):2254-63. DOI: 10.1111/j.1538-7836.2012.04905.x.
58. Clark P, Brennand J, Conkie JA, McCall F, Greer IA, Walker ID. Activated protein C sensitivity, protein C, protein S and coagulation in normal pregnancy. Thromb Haemost 1998;79(6):1166-70. (https://www.ncbi.nlm.nih.gov/pubmed/9657443).
59. Szecsi PB, Jorgensen M, Klajnbard A, Andersen MR, Colov NP, Stender S. Haemostatic reference intervals in pregnancy. Thromb Haemost 2010;103(4):718-27. DOI: 10.1160/TH09-10-0704.
60. Harrington LB, Marck BT, Wiggins KL, et al. Cross-sectional association of endogenous steroid hormone, sex hormone-binding globulin, and precursor steroid levels with hemostatic factor levels in postmenopausal women. J Thromb Haemost 2017;15(1):80-90. DOI: 10.1111/jth.13554.
61. Williams MS, Cushman M, Ouyang P, Heckbert SR, Kalyani RR, Vaidya D. Association of serum sex hormones with hemostatic factors in women on and off hormone therapy: The Multiethnic Study of Atherosclerosis. J Womens Health (Larchmt) 2016;25(2):166-72. DOI: 10.1089/jwh.2015.5465.
62. Sowers MR, Matthews KA, Jannausch M, et al. Hemostatic factors and estrogen during the menopausal transition. J Clin Endocrinol Metab 2005;90(11):5942-8. DOI: 10.1210/jc.2005-0591.
63. Steensma TD, Wensing-Kruger SA, Klink DT. How should physicians help gender-transitioning adolescents consider potential iatrogenic harms of hormone therapy? AMA J Ethics 2017;19(8):762-770. DOI: 10.1001/journalofethics.2017.19.8.ecas3-1708.
64. Iwamoto SJ, Defreyne J, Rothman MS, et al. Health considerations for transgender women and remaining unknowns: a narrative review. Ther Adv Endocrinol Metab 2019;10:2042018819871166. DOI: 10.1177/2042018819871166.
65. Kimberly LL, Folkers KM, Friesen P, et al. Ethical issues in gender-affirming care for youth. Pediatrics 2018;142(6). DOI: 10.1542/peds.2018-1537.
66. J Jarin J, Pine-Twaddell E, Trotman G, et al. Cross-sex hormones and metabolic parameters in adolescents with gender dysphoria. Pediatrics 2017;139(5). DOI: 10.1542/peds.2016-3173. PMID: 28557738.
67. Nokoff NJ, Scarbro SL, Moreau KL, et al. Body composition and markers of cardiometabolic health in transgender youth compared with cisgender youth. J Clin Endocrinol Metab 2020;105(3). DOI: 10.1210/clinem/dgz029.
68. Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic response to gender-affirming hormones among transgender youth. J Adolesc Health 2018;62(4):397-401. DOI: 10.1016/j.jadohealth.2017.08.005.
69. Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone development in transgender adolescents treated with gnrh analogues and subsequent gender-affirming hormones. J Clin Endocrinol Metab 2020;105(12). DOI: 10.1210/clinem/dgaa604.
70. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 2017;95:11-19. DOI: 10.1016/j.bone.2016.11.008.
71. Kowalczyk Mullins TL, Braverman PK, Dorn LD, Kollar LM, Kahn JA. Adolescent preferences for human immunodeficiency virus testing methods and impact of rapid tests on receipt of results. J Adolesc Health 2010;46(2):162-8. DOI: 10.1016/j.jadohealth.2009.06.015. PMID: 20113922.
72. Mullins TK, Braverman PK, Dorn LD, Kollar LM, Kahn JA. Adolescents' agreement to test for HIV when different testing methods are offered. Int J STD AIDS 2012;23(3):173-6. DOI: 10.1258/ijsa.2009.009035. PMID: 22581869.
73. Spicer B, Kahn JA, Zimet G, Qiu T, Huang B, Mullins TLK. U.S. physician intentions to recommend and prescribe HIV pre-exposure to adolescents and young adults. AIDS 2020 (abstract). Virtual due to COVID-19. 2020.
74. Mullins ES, Kombrinck KW, Talmage KE, et al. Genetic elimination of prothrombin in adult mice is not compatible with survival and results in spontaneous hemorrhagic events in both heart and brain. Blood 2009;113(3):696-704. DOI: 10.1182/blood-2008-07-169003. PMCID: PMC2628376.

75. Shaw MA, Gao Z, McElhinney KE, et al. Plasminogen deficiency delays the onset and protects from demyelination and paralysis in autoimmune neuroinflammatory disease. J Neurosci 2017;37(14):3776-3788. DOI: 10.1523/JNEUROSCI.2932-15.2017. PMCID: PMC5394895.
76. Silva LM, Lum AG, Tran C, et al. Plasmin-mediated fibrinolysis enables macrophage migration in a murine model of inflammation. Blood 2019;134(3):291-303. DOI: 10.1182/blood.2018874859. PMCID: PMC6639982.
77. Nasimuzzaman M, Arumugam PI, Mullins ES, et al. Elimination of the fibrinogen integrin alphaMbeta2-binding motif improves renal pathology in mice with sickle cell anemia. Blood Adv 2019;3(9):1519-1532. DOI: 10.1182/bloodadvances.2019032342. PMCID: PMC6517666.
78. Arumugam PI, Mullins ES, Shanmukhappa SK, et al. Genetic diminution of circulating prothrombin ameliorates multiorgan pathologies in sickle cell disease mice. Blood 2015;126(15):1844-55. DOI: 10.1182/blood-2015-01-625707. PMCID: PMC4600020.
79. Chowdary P, Mullins ES, Konkle BA, et al. Long-term safety and efficacy results from the phase 3b, open-label, multicentre Continuation study of rurioctocog alfa pegol for prophylaxis in previously treated patients with severe haemophilia A. Haemophilia 2020;26(4):e168-e178. DOI: 10.1111/hae.14052. PMID: 32597029.
80. Reipert BM, Gangadharan B, Hofbauer CJ, et al. The prospective Hemophilia Inhibitor PUP Study reveals distinct antibody signatures prior to FVIII inhibitor development. Blood Adv 2020;4(22):5785-5796. DOI: 10.1182/bloodadvances.2020002731. PMCID: PMC7686884.
81. Dunn AL, Ahuja SP, Mullins ES. Real-world experience with use of Antihemophilic Factor (Recombinant), PEGylated for prophylaxis in severe haemophilia A. Haemophilia 2018;24(3):e84-e92. DOI: 10.1111/hae.13403. PMID: 29359417.
82. Srivaths L, Minard CG, O'Brien SH, et al. The spectrum and severity of bleeding in adolescents with low von Willebrand factor-associated heavy menstrual bleeding. Blood Adv 2020;4(13):3209-3216. DOI: 10.1182/bloodadvances.2020002081. PMCID: PMC7362347.
83. Biro FM, Pajak A, Wolff MS, et al. Age of menarche in a longitudinal US cohort. J Pediatr Adolesc Gynecol 2018;31(4):339-345. DOI: 10.1016/j.jpag.2018.05.002. PMCID: PMC6121217.
84. Biro FM, Pinney SM, Schwartz RC, Huang B, Cattran AM, Haslam SZ. Amphiregulin as a novel serum marker of puberty in girls. J Pediatr Adolesc Gynecol 2017;30(5):535-539. DOI: 10.1016/j.jpag.2017.02.003. PMCID: PMC5559336.
85. Biro FM, Pinney SM, Huang B, Baker ER, Walt Chandler D, Dorn LD. Hormone changes in peripubertal girls. J Clin Endocrinol Metab 2014;99(10):3829-35. DOI: 10.1210/jc.2013-4528. PMCID: PMC4184081.
86. Biro FM, Huang B, Chandler DW, Fassler CL, Pinney SM. Impact of pubertal maturation and chronologic age on sex steroids in peripubertal girls. J Clin Endocrinol Metab 2019;104(7):2971-2977. DOI: 10.1210/jc.2018-02684. PMCID: PMC6546309.
87. Attfield KR, Pinney SM, Sjodin A, et al. Longitudinal study of age of menarche in association with childhood concentrations of persistent organic pollutants. Environ Res 2019;176:108551. DOI: 10.1016/j.envres.2019.108551. PMID: 31376650. PMC Journal - In Process.
88. Biro FM, Greenspan LC, Galvez MP, et al. Onset of breast development in a longitudinal cohort. Pediatrics 2013;132(6):1019-27. DOI: 10.1542/peds.2012-3773. PMCID: PMC3838525.
89. Wolff MS, Teitelbaum SL, McGovern K, et al. Phthalate exposure and pubertal development in a longitudinal study of US girls. Hum Reprod 2014;29(7):1558-66. DOI: 10.1093/humrep/deu081. PMCID: PMC4059333.
90. Biro FM, Huang B, Wasserman H, Gordon CM, Pinney SM. Pubertal growth, IGF-1, and windows of susceptibility: Puberty and future breast cancer risk. J Adolesc Health 2021;68(3):517-522. DOI: 10.1016/j.jadohealth.2020.07.016. PMCID: PMC7902462.
91. Tourdot BE, Stoveken H, Trumbo D, et al. Genetic variant in human PAR (Protease-Activated Receptor) 4 enhances thrombus formation resulting in resistance to antiplatelet therapeutics. Arterioscler Thromb Vasc Biol 2018;38(7):1632-1643. DOI: 10.1161/ATVBAHA.118.311112. PMCID: PMC6023764.
92. Tourdot BE, Adili R, Isingizwe ZR, et al. 12-HETrE inhibits platelet reactivity and thrombosis in part through the prostacyclin receptor. Blood Adv 2017;1(15):1124-1131. DOI: 10.1182/bloodadvances.2017006155. PMCID: PMC5728320.

93. Tourdot BE, Conaway S, Niisuke K, Edelstein LC, Bray PF, Holinstat M. Mechanism of race-dependent platelet activation through the protease-activated receptor-4 and Gq signaling axis. Arterioscler Thromb Vasc Biol 2014;34(12):2644-50. DOI: 10.1161/ATVBAHA.114.304249. PMCID: PMC4239175.
94. Trout AT, Anupindi SA, Gee MS, et al. Normal liver stiffness measured with MR Elastography in children. Radiology 2020;297(3):663-669. DOI: 10.1148/radiol.2020201513. PMCID: PMC7706876.
95. Gilligan LA, Davenport MS, Trout AT, et al. Risk of acute kidney injury following contrast-enhanced ct in hospitalized pediatric patients: A propensity score analysis. Radiology 2020;294(3):548-556. DOI: 10.1148/radiol.2020191931. PMCID: PMC7053230.
96. Siddiqui M, Judd EK, Dudenbostel T, et al. Masked uncontrolled hypertension is not attributable to medication nonadherence. Hypertension 2019;74(3):652-659. DOI: 10.1161/HYPERTENSIONAHA.119.13258. PMCID: PMC6687528.
97. Rahmani J, Haghighian Roudsari A, Bawadi H, et al. Relationship between body mass index, risk of venous thromboembolism and pulmonary embolism: A systematic review and dose-response meta-analysis of cohort studies among four million participants. Thromb Res 2020;192:64-72. DOI: 10.1016/j.thromres.2020.05.014.
98. Christiansen SC, Lijfering WM, Naess IA, et al. The relationship between body mass index, activated protein C resistance and risk of venous thrombosis. J Thromb Haemost 2012;10(9):1761-7. DOI: 10.1111/j.1538-7836.2012.04828.x.
99. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost 2003;89(3):493-8. (https://www.ncbi.nlm.nih.gov/pubmed/12624633).
100. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 1995;85(6):1504-8. (https://www.ncbi.nlm.nih.gov/pubmed/7888671).
101. Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med 2000;343(7):457-62. DOI: 10.1056/NEJM200008173430702.
102. Kraaijenhagen RA, in't Anker PS, Koopman MM, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. Thromb Haemost 2000;83(1):5-9. (https://www.ncbi.nlm.nih.gov/pubmed/10669145).
103. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996;88(10):3698-703. (https://www.ncbi.nlm.nih.gov/pubmed/8916933).
104. Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med 2009;169(6):610-5. DOI: 10.1001/archinternmed.2008.589.
105. Zoller B, Li X, Sundquist J, Sundquist K. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. Circulation 2011;124(9):1012-20. DOI: 10.1161/CIRCULATIONAHA.110.965020.
106. Couturaud F, Leroyer C, Julian JA, et al. Factors that predict risk of thrombosis in relatives of patients with unprovoked venous thromboembolism. Chest 2009;136(6):1537-1545. DOI: 10.1378/chest.09-0757.
107. Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA 1997;277(8):642-5. (https://www.ncbi.nlm.nih.gov/pubmed/9039882).
108. Hansson PO, Eriksson H, Welin L, Svardsudd K, Wilhelmsen L. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". Arch Intern Med 1999;159(16):1886-90. DOI: 10.1001/archinte.159.16.1886.
109. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994;344(8935):1453-7. DOI: 10.1016/s0140-6736(94)90286-0.
110. Khialani D, le Cessie S, Lijfering WM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. The joint effect of genetic risk factors and different types of combined oral contraceptives on venous thrombosis risk. Br J Haematol 2020;191(1):90-97. DOI: 10.1111/bjh.16666.
111. Allen AN, Jiao R, Day P, Pagels P, Gimpel N, SoRelle JA. Dynamic impact of hormone therapy on laboratory values in transgender patients over time. J Appl Lab Med 2021;6(1):27-40. DOI: 10.1093/jalm/jfaa192.

112. Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in referrals to a pediatric transgender clinic. Pediatrics 2019;144(5). DOI: 10.1542/peds.2019-1368.
113. Drotar DE. Promoting Adherence to Medical Treatment in Chronic Childhood Illness: Concepts, Methods, and Interventions: Psychology Press, 2000.
114. Morgan E, Moran K, Ryan DT, Mustanski B, Newcomb ME. Threefold increase in PrEP uptake over time with high adherence among young men who have sex with men in Chicago. AIDS Behav 2018;22(11):3637-3644. DOI: 10.1007/s10461-018-2122-5.
115. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials 2004;5(2):74-9. DOI: 10.1310/JFXH-G3X2-EYM6-D6UG.
116. Taddeo D, Egedy M, Frappier JY. Adherence to treatment in adolescents. Paediatr Child Health 2008;13(1):19-24. DOI: 10.1093/pch/13.1.19.
117. Zelikovsky N, Schast AP. Eliciting accurate reports of adherence in a clinical interview: development of the Medical Adherence Measure. Pediatr Nurs 2008;34(2):141-6. (https://www.ncbi.nlm.nih.gov/pubmed/18543839).
118. Taboada M, Santen R, Lima J, et al. Pharmacokinetics and pharmacodynamics of oral and transdermal 17beta estradiol in girls with Turner syndrome. J Clin Endocrinol Metab 2011;96(11):3502-10. DOI: 10.1210/jc.2011-1449.
119. Conklin SE, Knezevic CE. Advancements in the gold standard: Measuring steroid sex hormones by mass spectrometry. Clin Biochem 2020;82:21-32. DOI: 10.1016/j.clinbiochem.2020.03.008.
120. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem 1982;16(6):801-10. DOI: 10.1016/0022-4731(82)90038-3.
121. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84(10):3666-72. DOI: 10.1210/jcem.84.10.6079.
122. Torres-Santiago L, Mericq V, Taboada M, et al. Metabolic effects of oral versus transdermal 17beta-estradiol (E(2)): a randomized clinical trial in girls with Turner syndrome. J Clin Endocrinol Metab 2013;98(7):2716-24. DOI: 10.1210/jc.2012-4243.
123. Johnson KC, Aragaki AK, Jackson R, et al. Tissue Factor Pathway Inhibitor, Activated Protein C Resistance, and risk of coronary heart disease due to combined estrogen plus progestin therapy. Arterioscler Thromb Vasc Biol 2016;36(2):418-24. DOI: 10.1161/ATVBAHA.115.306905.
124. Wrzyszcz A, Urbaniak J, Sapa A, Wozniak M. An efficient method for isolation of representative and contamination-free population of blood platelets for proteomic studies. Platelets 2017;28(1):43-53. DOI: 10.1080/09537104.2016.1209478.
125. Maxwell JA. Designing a qualitative study. In: Bickman L and Roy R, ed. Handbook of Applied Social Research Methods.: Sage; 1998:69-100.
126. Chen D, Kolbuck VD, Sutter ME, Tishelman AC, Quinn GP, Nahata L. Knowledge, practice behaviors, and perceived barriers to fertility care among providers of transgender healthcare. J Adolesc Health 2019;64(2):226-234. DOI: 10.1016/j.jadohealth.2018.08.025.
127. Notini L, Pang KC, Telfer M, McDougall R. "No one stays just on blockers forever": Clinicians' divergent views and practices regarding puberty suppression for nonbinary young people. J Adolesc Health 2021;68(6):1189-1196. DOI: 10.1016/j.jadohealth.2020.09.028.
128. Badawy SM, Rychlik K, Sharathkumar AA. Current practice of pharmacological thromboprophylaxis for prevention of venous thromboembolism in hospitalized children: A survey of pediatric hemostasis and thrombosis experts in North America. J Pediatr Hematol Oncol 2016;38(4):301-7. DOI: 10.1097/MPH.0000000000000534.
129. Kavoussi PK, Machen GL, Wenzel JL, et al. Medical treatments for hypogonadism do not significantly increase the risk of deep vein thrombosis over general population risk. Urology 2019;124:127-130. DOI: 10.1016/j.urology.2018.11.009.
130. Li H, Benoit K, Wang W, Motsko S. Association between use of exogenous testosterone therapy and risk of venous thrombotic events among exogenous testosterone treated and untreated men with hypogonadism. J Urol 2016;195(4 Pt 1):1065-72. DOI: 10.1016/j.juro.2015.10.134.
131. Martinez C, Suissa S, Rietbrock S, et al. Testosterone treatment and risk of venous thromboembolism: population based case-control study. BMJ 2016;355:i5968. DOI: 10.1136/bmj.i5968.

132. Pyra M, Casimiro I, Rusie L, et al. An observational study of hypertension and thromboembolism among transgender patients using gender-affirming hormone therapy. Transgend Health 2020;5(1):1-9. DOI: 10.1089/trgh.2019.0061.
133. Bidlingmaier C, Kenet G, Kurnik K, et al. Safety and efficacy of low molecular weight heparins in children: a systematic review of the literature and meta-analysis of single-arm studies. Semin Thromb Hemost 2011;37(7):814-25. DOI: 10.1055/s-0031-1297173.
134. Acker GM. Transphobia among students majoring in the helping professions. J Homosex 2017;64(14):2011-2029. DOI: 10.1080/00918369.2017.1293404.
135. Shires DA, Prieto L, Woodford MR, Jaffee KD, Stroumsa D. Gynecologic health care providers' willingness to provide routine care and Papanicolaou tests for transmasculine individuals. Journal of Women's Health 2019;28:1487-1492.
136. Shires DA, Stroumsa D, Jaffee KD, Woodford MR. Primary care clinicians' willingness to care for transgender patients. Ann Fam Med 2018;16(6):555-558. DOI: 10.1370/afm.2298.
137. Guss CE, Woolverton GA, Borus J, Austin SB, Reisner SL, Katz-Wise SL. Transgender adolescents' experiences in primary care: A qualitative study. J Adolesc Health 2019;65(3):344-349. DOI: 10.1016/j.jadohealth.2019.03.009.
138. Fix L, Durden M, Obedin-Maliver J, et al. Stakeholder perceptions and experiences regarding access to contraception and abortion for transgender, non-binary, and gender-expansive individuals assigned female at birth in the U.S. Arch Sex Behav 2020;49(7):2683-2702. DOI: 10.1007/s10508-020-01707-w.
139. Gridley SJ, Crouch JM, Evans Y, et al. Youth and caregiver perspectives on barriers to gender-affirming health care for transgender youth. J Adolesc Health 2016;59(3):254-261. DOI: 10.1016/j.jadohealth.2016.03.017.
140. Knight RE, Shoveller JA, Carson AM, Contreras-Whitney JG. Examining clinicians' experiences providing sexual health services for LGBTQ youth: considering social and structural determinants of health in clinical practice. Health Educ Res 2014;29(4):662-70. DOI: 10.1093/her/cyt116.
141. McPhail D, Rountree-James M, Whetter I. Addressing gaps in physician knowledge regarding transgender health and healthcare through medical education. Can Med Educ J 2016;7(2):e70-e78. (https://www.ncbi.nlm.nih.gov/pubmed/28344694).
142. Stroumsa D, Shires DA, Richardson CR, Jaffee KD, Woodford MR. Transphobia rather than education predicts provider knowledge of transgender health care. Med Educ 2019;53(4):398-407. DOI: 10.1111/medu.13796.
143. Hines DD, Laury ER, Habermann B. They just don't get me: A qualitative analysis of transgender women's health care experiences and clinician interactions. J Assoc Nurses AIDS Care 2019;30(5):e82-e95. DOI: 10.1097/JNC.0000000000000023.
144. Montaño DE, Kasprzyk D. Theory of reasoned action, theory of planned behavior, and the integrated behavior model. In: Glanz K, Rimer B, Viswanath K, eds. Health Behavior and Health Education: Theory, Research, and Practice. 4th ed. San Francisco: Jossey-Bass; 2008:67-96.
145. Kahn JA, Cooper HP, Vadaparampil ST, et al. Human papillomavirus vaccine recommendations and agreement with mandated human papillomavirus vaccination for 11-to-12-year-old girls: a statewide survey of Texas physicians. Cancer Epidemiol Biomarkers Prev 2009;18(8):2325-32. PMID:19661092. DOI: 18/8/2325 [pii]10.1158/1055-9965.EPI-09-0184.
146. Kahn JA, Zimet GD, Bernstein DI, et al. Pediatricians' intention to administer human papillomavirus vaccine: the role of practice characteristics, knowledge, and attitudes. J Adolesc Health 2005;37(6):502-10. PMID:16310128. DOI: S1054-139X(05)00373-[pii]10.1016/j.jadohealth.2005.07.014.
147. Millstein SG, Igra V, Gans J. Delivery of STD/HIV preventive services to adolescents by primary care physicians. J Adolesc Health 1996;19(4):249-57. PMID:8897102. DOI: S1054-139X(96)00092-4 [pii]10.1016/S1054-139X(96)00092-4.
148. Riedesel JM, Rosenthal SL, Zimet GD, et al. Attitudes about human papillomavirus vaccine among family physicians. J Pediatr Adolesc Gynecol 2005;18(6):391-8. PMID:16338604. DOI: S1083-3188(05)00159-2 [pii]10.1016/j.jpag.2005.09.004.
149. Godin G, Belanger-Gravel A, Eccles M, Grimshaw J. Healthcare professionals' intentions and behaviours: a systematic review of studies based on social cognitive theories. Implementation science : IS 2008;3:36. DOI: 10.1186/1748-5908-3-36.

150. Millstein SG. Utility of the theories of reasoned action and planned behavior for predicting physician behavior: a prospective analysis. Health Psychol 1996;15(5):398-402. PMID:8891719. (http://www.ncbi.nlm.nih.gov/pubmed/8891719).
151. Perkins MB, Jensen PS, Jaccard J, et al. Applying theory-driven approaches to understanding and modifying clinicians' behavior: what do we know? Psychiatr Serv 2007;58(3):342-8. DOI: 10.1176/appi.ps.58.3.342.
152. Kahn JA, Rosenthal SL, Tissot AM, Bernstein DI, Wetzel C, Zimet GD. Factors influencing pediatricians' intention to recommend human papillomavirus vaccines. Ambul Pediatr 2007;7(5):367-73. PMID:17870645. DOI: S1530-1567(07)00097-4 [pii]10.1016/j.ambp.2007.05.010.
153. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Brugess R, eds. Analyzing Qualitative Data: Routledge; 1994:731-194.
154. Kuzel A. Sampling in qualitative inquiry. In: Crabtree B, Miller W, eds. Doing Qualitative Research: Sage; 2009:33-45.
155. Warren AR, Steffen AM. Development of a Transgender and Gender Nonconforming Language Self-Efficacy Scale for social service providers working with older adults. J Appl Gerontol 2020;39(5):555-560. DOI: 10.1177/0733464818759754.
156. Nagoshi JL, Adams KA, Terrell HK, Hill ED, Brzuzy S, Nagoshi CT. Gender differences in correlates of homophobia and transphobia. Sex Roles 2008;59:521-531.
157. Ali N, Fleisher W, Erickson J. Psychiatrists' and psychiatry residents' attitudes toward transgender people. Acad Psychiatry 2016;40(2):268-73. DOI: 10.1007/s40596-015-0308-y.
158. Billard TJ. The crisis in content validity among existing measures of transphobia. Arch Sex Behav 2018;47(5):1305-1306. DOI: 10.1007/s10508-018-1191-x.
159. Hill DB, Willoughby BLB. The development and validation of the Genderism and Transphobia Scale. Sex Roles 2005;53:531-544.
160. Billard TJ. Attitudes Toward Transgender Men and Women: Development and validation of a new measure. Front Psychol 2018;9:387. DOI: 10.3389/fpsyg.2018.00387.
161. Walch SE, Ngamake ST, Francisco J, Stitt RL, Shingler KA. The attitudes toward transgendered individuals scale: psychometric properties. Arch Sex Behav 2012;41(5):1283-91. DOI: 10.1007/s10508-012-9995-6.
162. Dillman D, Smyth J, Christian L. Internet, Mail, and Mixed-Model Surveys: The Tailored Design Method. 3rd ed: John Wiley & Sons, Inc; 2009:221-227.
163. Dillman D, Smyth J, Christian L. Internet, Mail, and Mixed-Model Surveys: The Tailored Design Method. 3rd ed: John Wiley & Sons, Inc; 2009:228-230.
164. Willis GB. Cognitive Interviewing: A Tool for Improving Questionnaire Design. Thousand Oaks, CA: Sage, 2005. Page 161.
165. Knafl K, Deatrick J, Gallo A, et al. The analysis and interpretation of cognitive interviews for instrument development. Res Nurs Health 2007;30(2):224-34. DOI: 10.1002/nur.20195.
166. Alreck PL, Settle RB. The Survey Research Handbook. 3rd ed. Boston: Mc-Graw Hill Irwin, 2004; pages 292-295.
167. Aday LA, Cornelius LJ. Designing and Conducting Health Surveys. San Francisco: Jossey-Bass; 2006:66-68.
168. VanGeest JB, Johnson TP, Welch VL. Methodologies for improving response rates in surveys of physicians: a systematic review. Eval Health Prof 2007;30(4):303-21. DOI: 10.1177/0163278707307899.
169. Dillman D, Smyth J, Christian L. Internet, Mail, and Mixed-Model Surveys: The Tailored Design Method. 3rd ed: John Wiley & Sons, Inc; 2009:300-330.
170. McMahon SR, Iwamoto M, Massoudi MS, et al. Comparison of e-mail, fax, and postal surveys of pediatricians. Pediatrics 2003;111(4 Pt 1):e299-303. PMID:12671142. (http://www.ncbi.nlm.nih.gov/pubmed/12671142).
171. Dillman D, Smyth J, Christian L. Internet, Mail, and Mixed-Model Surveys: The Tailored Design Method. 3rd ed: John Wiley & Sons, Inc; 2009:259-260.
172. Daley MF, Liddon N, Crane LA, et al. A national survey of pediatrician knowledge and attitudes regarding human papillomavirus vaccination. Pediatrics 2006;118(6):2280-9. PMID:17142510. DOI: 118/6/2280 [pii]10.1542/peds.2006-1946.

173. Sable MR, Schwartz LR, Kelly PJ, Lisbon E, Hall MA. Using the theory of reasoned action to explain physician intention to prescribe emergency contraception. Perspect Sex Reprod Health 2006;38(1):20-7. PMID:16554268. DOI: 3802006 [pii]10.1363/psrh.38.020.06.
174. Brown KS, Steinauer JE, Turk J, Landy U, Jackson AV. Racial diversity in abortion education and intention to provide abortion in postresidency practice: data from the Ryan Program. Am J Obstet Gynecol 2020;222(3):271 e1-271 e8. DOI: 10.1016/j.ajog.2019.09.009.
175. Cunningham-Erves J, Forbes L, Ivankova N, Mayo-Gamble T, Kelly-Taylor K, Deakings J. Black mother's intention to vaccinate daughters against HPV: A mixed methods approach to identify opportunities for targeted communication. Gynecol Oncol 2018;149(3):506-512. DOI: 10.1016/j.ygyno.2018.03.047.
176. Kahn JA, Ding L, Huang B, Zimet GD, Rosenthal SL, Frazier AL. Mothers' intention for their daughters and themselves to receive the human papillomavirus vaccine: a national study of nurses. Pediatrics 2009;123(6):1439-45. DOI: 10.1542/peds.2008-1536.
177. Ogilvie GS, Gordon S, Smith LW, et al. Intention to receive a COVID-19 vaccine: results from a population-based survey in Canada. BMC Public Health 2021;21(1):1017. DOI: 10.1186/s12889-021-11098-9.
178. Peterson EL, Pidano AE, Honigfeld L. Pediatric primary care providers' reported likelihood to refer to mental health specialists. Fam Syst Health 2018;36(3):410-414. DOI: 10.1037/fsh0000335.
179. DeVellis RF. Scale Development: Theory and Applications. Newbury Park, CA: Sage, 1991. Page 107.
180. Aday LA, Cornelius LJ. Designing and Conducting Health Surveys. San Francisco: Jossey-Bass; 2006:62.
181. Teixeira-Pinto A, Normand SL. Correlated bivariate continuous and binary outcomes: issues and applications. Stat Med 2009;28(13):1753-73. DOI: 10.1002/sim.3588.
182. Teixeira-Pinto A, Siddique J, Gibbons R, Normand SL. Statistical approaches to modeling multiple outcomes in psychiatric studies. Psychiatr Ann 2009;39(7):729-735. DOI: 10.3928/00485713-20090625-08.
183. Aday LA, Cornelius LJ. Designing and Conducting Health Surveys. San Francisco: Jossey-Bass; 2006:178-181.
184. Streiff MB, Smith B, Spivak JL. The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: a survey of American Society of Hematology members' practice patterns. Blood 2002;99(4):1144-9. DOI: 10.1182/blood.v99.4.1144.
185. Vesely SK, Buchanan GR, Adix L, et al. Self-reported initial management of childhood idiopathic thrombocytopenic purpura: results of a survey of members of the American Society of Pediatric Hematology/Oncology, 2001. J Pediatr Hematol Oncol 2003;25(2):130-3. DOI: 10.1097/00043426-200302000-00009.
186. Harris C, Katkin J, Cataletto M, Dorkin H, Laskosz L, Ruch-Ross H. US pediatric pulmonology workforce. Pediatr Pulmonol 2019;54(4):444-450. DOI: 10.1002/ppul.24253.
187. Hurley L, Kempe A, Crane LA, et al. Care of undocumented individuals with ESRD: a national survey of US nephrologists. Am J Kidney Dis 2009;53(6):940-9. DOI: 10.1053/j.ajkd.2008.12.029.
188. Larenas-Linnemann DE, Hauswirth DW, Calabria CW, Sher LD, Rank MA. American Academy of Allergy, Asthma & Immunology membership experience with allergen immunotherapy safety in patients with specific medical conditions. Allergy Asthma Proc 2016;37(5):112-22. DOI: 10.2500/aap.2016.37.3981.
189. Smallridge RC, Diehl N, Bernet V. Practice trends in patients with persistent detectable thyroglobulin and negative diagnostic radioiodine whole body scans: a survey of American Thyroid Association members. Thyroid 2014;24(10):1501-7. DOI: 10.1089/thy.2014.0043.
190. Cook DA, Wittich CM, Daniels WL, West CP, Harris AM, Beebe TJ. Incentive and reminder strategies to improve response rate for Iinternet-based physician surveys: A randomized experiment. J Med Internet Res 2016;18(9):e244. DOI: 10.2196/jmir.6318.
191. Lu KH, George JN, Vesely SK, Terrell DR. Management of primary immune thrombocytopenia, 2012: a survey of Oklahoma hematologists-oncologists. Am J Med Sci 2014;347(3):190-4. DOI: 10.1097/MAJ.0b013e31827f4dd1.
192. Masselink LE, Erikson CE, Connell NT, et al. Associations between hematology/oncology fellows' training and mentorship experiences and hematology-only career plans. Blood Adv 2019;3(21):3278-3286. DOI: 10.1182/bloodadvances.2019000569.

193. Aday LA, Cornelius LJ. Designing and Conducting Health Surveys. San Francisco: Jossey-Bass; 2006:173-174.
194. Dillman D, Smyth J, Christian L. Internet, Mail, and Mixed-Model Surveys: The Tailored Design Method. 3rd ed: John Wiley & Sons, Inc; 2009:238-242.
195. Halpern SD, Ubel PA, Berlin JA, Asch DA. Randomized trial of 5 dollars versus 10 dollars monetary incentives, envelope size, and candy to increase physician response rates to mailed questionnaires. Med Care 2002;40(9):834-9. DOI: 10.1097/01.MLR.0000024722.29926.3D.
196. VanGeest JB, Wynia MK, Cummins DS, Wilson IB. Effects of different monetary incentives on the return rate of a national mail survey of physicians. Med Care 2001;39(2):197-201. (http://www.ncbi.nlm.nih.gov/pubmed/11176557).
197. Goritz AS. Incentives in web studies: Methodological issues and a review. Int J Internet Sci 2006;1:58-70.
198. Aday LA, Cornelius LJ. Designing and Conducting Health Surveys. San Francisco: Jossey-Bass; 2006:350-351.
199. Axinn WG, Pearce LD. Mixed Method Data Collection Strategies. New York: Cambridge University Press, 2006.
200. Zeller RA. Combining qualitative and quantitative techniques to develop culturally sensitive measures. In: Ostrow DG, Kessler RC, eds. Methodological Issues in AIDS Behavioral Research. New York: Plenum Press; 1993.
201. Gallagher ZJ, Fleetwood S, Kirley TL, et al. Heparin mimic material derived from cellulose nanocrystals. Biomacromolecules 2020;21(3):1103-1111. DOI: 10.1021/acs.biomac.9b01460. PMID: 32003977.
202. Dalton E, Chai Q, Shaw MW, McKenzie TJ, Mullins ES, Ayres N. Hydrogel-coated polyurethane/urea shape memory polymer foams. Journal of Polymer Science Part A: Polymer Chemistry 2019;57(13):1389-1395. DOI: https://doi.org/10.1002/pola.29398. Not indexed in PubMed.
203. Huang Y, Shaw MA, Warmin MR, Mullins ES, Ayres N. Blood compatibility of heparin-inspired, lactose containing, polyureas depends on the chemistry of the polymer backbone. Polymer Chemistry 2016;7(23):3897-3905. (10.1039/C6PY00616G). DOI: 10.1039/C6PY00616G. Not indexed in PubMed.
204. Huang Y, Shaw MA, Mullins ES, Kirley TL, Ayres N. Synthesis and anticoagulant activity of polyureas containing sulfated carbohydrates. Biomacromolecules 2014;15(12):4455-66. DOI: 10.1021/bm501245v. PMCID: PMC4261991.
205. Office of Disease Prevention and Health Promotion, U.S. Department of Health and Human Services.. Healthy People 2020: Adolescent Health. Available online at: https://www.healthypeople.gov/2020/topics-objectives/topic/Adolescent-Health). Accessed on 10/24/21.
206. Arnold JD, Sarkodie EP, Coleman ME, Goldstein DA. Incidence of venous thromboembolism in transgender women receiving oral estradiol. J Sex Med 2016;13(11):1773-1777. DOI: 10.1016/j.jsxm.2016.09.001.
207. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertil Steril 2010;93(4):1267-72. DOI: 10.1016/j.fertnstert.2008.12.017.
208. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997;47(3):337-42. DOI: 10.1046/j.1365-2265.1997.2601068.x.
209. Wierckx K, Van Caenegem E, Schreiner T, et al. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. J Sex Med 2014;11(8):1999-2011. DOI: 10.1111/jsm.12571.
210. Asscheman H, Gooren LJ, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. Metabolism 1989;38(9):869-73. DOI: 10.1016/0026-0495(89)90233-3.
211. United States Census Bureau. Quick Facts - 2019. Available online at: https://www.census.gov/quickfacts/fact/table/US/PST045219. Accessed on 10/24/21.
212. Association of American Medical Colleges. Diversity in Medicine: Facts and Figures 2019. Available online at: https://www.aamc.org/data-reports/workforce/report/diversity-medicine-facts-and-figures-2019. Accessed on 10/24/21.
213. Olson-Kennedy J, Chan YM, Garofalo R, et al. Impact of early medical treatment for transgender youth: Protocol for the longitudinal, observational Trans Youth Care Study. JMIR Res Protoc 2019;8(7):e14434. DOI: 10.2196/14434.

214. Owen-Smith AA, Woodyatt C, Sineath RC, et al. Perceptions of barriers to and facilitators of participation in health research among transgender people. Transgend Health 2016;1(1):187-196. DOI: 10.1089/trgh.2016.0023.
215. Reisner SL, Chaudhry A, Cooney E, Garrison-Desany H, Juarez-Chavez E, Wirtz AL. 'It all dials back to safety': A qualitative study of social and economic vulnerabilities among transgender women participating in HIV research in the USA. BMJ Open 2020;10(1):e029852. DOI: 10.1136/bmjopen-2019-029852.
216. Staples JM, Bird ER, Masters TN, George WH. Considerations for culturally sensitive research with transgender adults: A qualitative analysis. J Sex Res 2018;55(8):1065-1076. DOI: 10.1080/00224499.2017.1292419.
217. Willis GB. Cognitive Interviewing: A Tool for Improving Questionnaire Design. Thousand Oaks, CA: Sage, 2005.

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September 10, 2021

Tanya L.K. Mullins, MD, MS
Associate Professor of Pediatrics
Director of Research, Division of Adolescent and Transition Medicine
Cincinnati Children's Hospital Medical Center

Dear Tanya:

I am writing in enthusiastic support of your R01 proposal titled "Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy". I am excited to participate in this important proposal as a Co-Investigator. As you know, at Cincinnati Children's Hospital Medical Center, we have a growing number of transgender patients. With regards to their hematologic care, especially with concerns regarding thrombosis with estradiol gender-affirming hormone therapy (GAHT), there is a lack of data that would help hematologists such as myself care for these patients. In my own division, there are different approaches to care of these patients.

To begin to lay a foundation of data for care of these patients, I collaborated with you and (b)(6) (b)(6) to conduct a retrospective review of all patients seen in the Transgender Health Center during its first 7 years. We identified 611 youth who had initiated GAHT since the clinic's inception. It was striking that a majority of these individuals had preexisting risk factors for thrombosis, including obesity, tobacco use, family and/or personal history of thrombosis, and/or pro-thrombotic laboratory abnormalities. While we did not observe any thromboses in this cohort, there was a very limited follow-up time for many of the patients in the study. It was clear from this review that additional data is needed to inform care of transgender patients.

As you know, my career has focused on understanding the basic biology of hemostatic factors, both in coagulation and in other physiologic and pathologic disease processes. As (b)(6) (b)(6) I have been the local PI for many multi-center clinical research studies. This work has resulted in multiple publications, including first and senior author publications. Thus, I have also had significant experience with running clinical trials. As you know, estrogen induces changes within the hemostatic system that increase thrombin generation and increase platelet count and reactivity. My laboratory is proficient in molecular studies of coagulation factors, including those planned in this R01 proposal, and has the needed equipment to conduct these studies. I will collaborate with (b)(6) to examine the effect of estradiol on platelet activation. I will directly oversee all laboratory studies conducted in the first aim of this proposal. I will also collaborate with you and (b)(6) to analyze and disseminate the data generated from this proposal.

I eagerly look forward to collaborating with you on this important and exciting work!

Sincerely,

(b)(6)

Associate Professor of Pediatrics
University of Cincinnati - College of Medicine
(b)(6)
Division of Hematology
Cancer and Blood Diseases Institute
Cincinnati Children's Hospital Medical Center

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September 17, 2021

Tanya L.K. Mullins, MD, MS
Associate Professor of Pediatrics
Director of Research, Division of Adolescent and Transition Medicine
Cincinnati Children's Hospital Medical Center

(b)(6) MD
Associate Professor of Pediatrics
(b)(6)
Division of Hematology
Cincinnati Children's Hospital Medical Center

Dear Tanya and (b)(6)

I am delighted to serve as a collaborator for your R01 submission entitled "Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy." As transgender and gender nonconforming youth continue to seek care and hormonal intervention, it is clear that better quality data is needed to determine the thrombosis risk of estradiol use in gender-affirming hormone therapy. There is little data to guide patients, families, and clinical caregivers, especially for those having risk for thrombosis prior to starting gender-affirming hormone therapy.

Over my career, I have developed expertise in sex hormones during pubertal development. I was the Cincinnati principal investigator for the Breast Cancer and the Environment Research Program, an NCI-funded longitudinal study for which I have authored 45 peer-reviewed publications to date. This study focused on environmental factors impacting sexual development in girls and young women and the potential impact of these factors on future cancer risk. I have significant expertise in normal pubertal development and hormonal changes in adolescence. I will be happy to provide expertise on measurement of sex hormones in your study and interpretations of changes in hormone levels.

As you know, I also have significant experience conducting longitudinal studies. In the first iteration of our study, we followed participants every 6 months for 6 years. In the extension study, we followed participants annually for another 5 years. Despite the long-term nature of this study, we had excellent retention of 64% of original recruits across the entirety of the two studies, over the course of 11 years. Given this experience, I have significant expertise in planning and conducting longitudinal studies of youth, including the strategies that enhance subject retention. I will also be glad to provide my expertise on recruitment and retention strategies.

I am delighted to serve as a collaborator on this important and timely proposal, and I will commit (b)(6) effort to this project for the first 3 years of the proposal, during which subjects will be recruited and retained in the study. I believe that this is a critically important study to generate the vital data needed to understand the impact of estradiol on coagulation and the implications for thrombosis risk. I look forward to collaborating with both of you, and to the results of this exciting study.

Sincerely,

(b)(6)

Professor of Pediatrics
University of Cincinnati - College of Medicine
Division of Adolescent and Transition Medicine
Cincinnati Children's Hospital Medicine Center

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September 17, 2021

Tanya L.K. Mullins, MD, MS
Associate Professor of Pediatrics
Director of Research, Division of Adolescent and Transition Medicine
Cincinnati Children's Medical Center

(b)(6) MD
Associate Professor of Pediatrics
(b)(6)
Division of Hematology
Cincinnati Children's Medical Center

Dear Tanya and (b)(6)

I am writing to express my enthusiastic support for the resubmission of your R01 entitled "Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy." As you know, there is a lack of information regarding the risk of thrombosis with estradiol gender-affirming hormone therapy (GAHT), especially in the adolescent and young adult population. Our previous collaboration has already resulted in a significant contribution to the literature, a baseline description of the thrombosis risk of the 611 patients previously started on GAHT at Cincinnati Children's Hospital Medical Center (CCHMC). This 2021 *Pediatrics* publication detailed the baseline thrombosis risk in our adolescent and young adult cohort at CCHMC. Based on this data, we know that the majority of our patients have multiple risk factors of thrombosis, even prior to starting estradiol GAHT.

As you know, I have been (b)(6) of the multidisciplinary Transgender Health Center at CCHMC since its inception in 2013. Since that time, we have had a significant number of new patients who present for evaluation each year. This demand even continued in 2020, despite the limitations due to the pandemic. Over the last three years, we have averaged 310 new consults per year. Over the last year of the chart review just completed, we initiated approximately 60 new patients on estradiol GAHT.

Given the importance of this work, I am happy to have enrollment of patients starting estradiol for GAHT from the Transgender Health Center. Indeed, my team will help to facilitate engagement with this study in any way possible. I believe that this study will help answer key questions regarding the thrombosis risk posed by estradiol GAHT for thrombosis and define the hemostatic changes associated with initiation of estradiol, which will in turn improve clinical care for this population.

I look forward to the results of this exciting research project!

Sincerely,
(b)(6)

Associate Professor of Pediatrics
(b)(6) Transgender Health Center
Division of Adolescent Medicine and Transition Medicine
Cincinnati Children's Hospital Medical Center

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September 17, 2021

Tanya L.K. Mullins, MD, MS
Associate Professor of Pediatrics
Director of Research, Division of Adolescent and Transition Medicine
Cincinnati Children's Medical Center

(b)(6) MD
Associate Professor of Pediatrics
(b)(6)
Division of Hematology
Cincinnati Children's Medical Center

Dear Tanya and (b)(6)

I am excited to collaborate with you on your R01 submission entitled "Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy." As you know, estradiol containing gender-affirming hormone therapy (GAHT) has been previously found to be associated with both venous and arterial thrombosis in adult transgender women. While the effects of estrogen-containing contraceptives and hormone replacement on coagulation factors has been previously studied, the effect of estrogen on platelet function has been less well-characterized. However, a recent study has suggested evidence of a gender-based differential in platelet activation. No studies have been conducted to assess the impact of estradiol on platelet function.

My laboratory is focused on platelet biology. We have specifically focused on the role of a common polymorphism in protease-activated receptor 4 in differential platelet activation. We have also studied the role of lipoxygenase in the modification of platelet activation. I, and my laboratory personnel, have significant experience in examining platelet activation by either light-transmission aggregometry or by whole blood FACS analysis. The studies proposed within this R01 are well within my area of expertise. I am happy to collaborate with you on running these studies. I will have (b)(6) committed effort in years 2-5 of this project, which corresponds to the years that samples will be available for analysis.

In summary, your proposal is an important study to determine if estradiol GAHT has a significant impact on the reactivity of platelets that may place transgender individuals at greater risk for thrombosis. I look forward to this study and the results that come from it.

Sincerely,

(b)(6)

Assistant Professor of Pediatrics
Division of Experimental Hematology and Cancer Biology
Cincinnati Children's Hospital Medical Center

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September 17, 2021

Tanya L.K. Mullins, MD, MS
Associate Professor of Pediatrics
Director of Research, Division of Adolescent and Transition Medicine
Cincinnati Children's Medical Center

(b)(6) MD
Associate Professor of Pediatrics
(b)(6)
Division of Hematology
Cincinnati Children's Medical Center

Dear Tanya and (b)(6)

I look forward to collaborating with you on your R01 resubmission entitled "Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy." There is a lack of data on the thrombosis risk of estradiol for gender-affirming hormone therapy (GAHT), especially in the adolescent and young adult population. Given the importance of GAHT in preventing suicide in transgender individuals, this is a needed study.

As you know, I am a member of the Division of Biostatics and Epidemiology at Cincinnati Children's Hospital Medical Center. I have significant experience with statistical analysis of longitudinal studies. I have provided statistical support and analysis for multiple grants funded by NIH in the setting of cancer, hypertension, steatohepatitis, and asthma. Based on our initial work, I have performed the power calculations for your R01 submission and resubmission, consulted on the data analysis plans, and worked with you to revise the data analysis plans and sample size calculations. My role will be to lead the development and implementation of the statistical analysis plan, review data management policies and practices, as well as conduct data analysis and generate study reports. I will work with you and the other co-investigators with statistical and design-related issues throughout all phases of the project.

I look forward to the results of these important studies. Your work has a likelihood of impacting the treatment of many transgender patients.

Sincerely,

(b)(6)

Professor of Pediatrics
Division of Biostatistics and Epidemiology
Cincinnati Children's Hospital Medical Center

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September 10, 2021

Tanya L.K. Mullins, MD, MS
Associate Professor of Pediatrics
Director of Research, Division of Adolescent and Transition Medicine
Cincinnati Children's Medical Center

(b)(6) MD
Associate Professor of Pediatric
(b)(6)
Division of Hematology
Cincinnati Children's Medical Center

Dear (b)(6)

I am writing to verify the willingness of our laboratory to support your R01 entitled "Thrombosis Risk in Transgender Adolescents and Young Adults Starting Gender-Affirming Hormone Therapy". As you know, I am the (b)(6) for the Cancer and Blood Diseases Institute (CBDI) Clinical Laboratories, including the Hemostasis-Thrombosis Laboratory (HTL). This laboratory provides specialty coagulation testing for both Cincinnati Children's Hospital Medical Center and serves as a referral laboratory for the community. Within the clinical laboratory assays that are routinely performed within the HTL for patient care are: protein C and S activities, free protein S, von Willebrand antigen, and von Willebrand ristocetin cofactor activity. The HTL has expert technical staff with many years of experience in coagulation testing.

Our laboratory has more than adequate capacity to run your study samples in addition to the standard clinical samples that are performed there. As you know, I have provided you with the estimates for performing these assays.

We look forward to working with you on this project.

Sincerely,

(b)(6)

(b)(6)
Cancer and Blood Diseases Institute
Cincinnati Children's Hospital Medical Center

AUTHENTICATION OF KEY RESOURCES

Animal lines: Not applicable

Cell Lines: Not applicable

Antibodies: All antibodies (including paired antibodies used in ELISA) used in these studies will be purchased commercially, and the manufacturer and product number will be noted in publications arising from this research.

Reagents: Chromogenic substrates used in quantification of coagulation will be purchased commercially, and manufacturer and product number will be noted in published works arising from this research. Reagents for thrombin generation assays will also be purchased commercially (ThermoFisher), and the product numbers will be noted in future publications.

Pharmaceuticals: Not applicable

APPENDIX 1

Specific Aim 2: Characterize the attitudes, practices, and intentions of hematologists caring for youth toward recommending thromboprophylaxis to transgender youth with personal/family risk factors that increase thrombosis risk.

Draft Interview Content for Interviews with Hematologists to Assess Attitudes toward Thromboprophylaxis in Transgender (TG) Youth (Aim 2, Phase 1)

Construct	Interview Questions
Opening	***Thank you for agreeing to be in this study. I appreciate your time and your interest in participating. For the purposes of this interview, "adolescent" will refer to anyone ages 13 through 17 years, and "young adult" will refer to anyone ages 18 through 22 years. As we go along, I will use the term "transgender" to refer to transgender, non-binary, gender nonconforming, or gender expansive youth.***
Demographics	***First, I'd like to ask some basic information about you.*** 1. What is your age? 2. How would you describe your race/ethnicity? 3. What is your area of specialty? **PROBE:** Pediatrics? Internal medicine? Combined medicine/pediatrics? Hematology? 4. What year did you graduate from medical school? 5. In what state did you complete your fellowship or highest level of training?
Practice characteristics	***Next, let's talk a little about your clinical practice.*** 6. How many adolescents ages 13-17 years would you estimate that you see over the average week? 7. How many young adults ages 18-22 years would you estimate that you see over the average week? 8. In your medical practice, have you provided medical care to transgender adolescents age 13-17 years? 9. In your medical practice, have you provided medical care to transgender young adults age 18-22 years? 10. How many transgender adolescents (ages 13-17 years) would you estimate that you have in your practice currently? How many transgender young adults (ages 18-22 years)?
Knowledge about and comfort with transgender health care	***Next, I'd like to learn about your knowledge and comfort with caring for transgender patients.*** 11. Have you ever had training or education in providing health care to transgender youth? **If yes**: What type of training was it (i.e., online, at a conference, grand rounds, self-directed reading, etc.)? In what level(s) of medical training were you when you had this education in transgender care?

	12. How would you rate your comfort in caring for transgender youth in general? **Probe**: Not at all comfortable, somewhat comfortable, very comfortable 13. How would you rate your familiarity with the gender transition process? **Probe:** Not at all familiar, Somewhat familiar, Very familiar 14. How would you rate your understanding of different gender terms, such as non-binary, transgender man, transgender woman, agender, etc.? 15. How confident are you that you could ask a youth about his/her/their gender? **Probe**: Not at all confident, somewhat confident, very confident 16. How confident are you that you could ask a youth about his/her/their preferred name? **Probe**: Not at all confident, somewhat confident, very confident 17. How confident are you that you could ask a youth about preferred pronouns (like she, he, they, ze, etc.?) **Probe**: Not at all confident, somewhat confident, very confident 18. What interventions would improve your comfort and confidence with caring for transgender youth?
Experiences with transgender patients and thrombopro-phylaxis	***Next, I'd like to learn a little about your experiences with seeing transgender patients who are referred to you for evaluation. For the next few questions, I'd like to talk about recommending thromboprophylaxis as different than prescribing.*** 19. Have you ever ***recommended*** thromboprophylaxis to a transgender adolescent age 13-17 years taking or about to start gender-affirming hormone therapy? **If yes**: - Could you describe what elements of the patient's history or laboratory results informed this recommendation? - Could you describe what the conversation was like? - How was the recommendation received by the patient and family? - Did the patient accept the recommendation? Did the family? 20. Have you ever ***prescribed*** thromboprophylaxis to a transgender adolescent age 13-17 years taking or about to start gender-affirming hormone therapy? **If yes:** **-** What medication did you start? - What was your goal duration of treatment? - Did the patient adhere to the treatment plan as prescribed? - Has the patient had any adverse events related to the thromboprophylaxis regimen, such as bleeding events? 21. Have you ever ***recommended*** thromboprophylaxis to a transgender young adult age 18-22 years taking or about to start gender-affirming hormone therapy? **If yes**: - Could you describe what elements of the patient's history or laboratory results informed this recommendation? - Could you describe what the conversation was like? - How was the recommendation received by the patient and family? - Did the patient accept the recommendation? Did the family?

	22. Have you ever ***prescribed*** thromboprophylaxis to a transgender young adult age 18-22 years taking or about to start gender affirming-hormone therapy? **If yes:** **-** What medication did you start? - What was your goal duration of treatment? - Did the patient adhere to the treatment plan as prescribed? - Has the patient had any adverse events related to the thromboprophylaxis regimen, such as bleeding events?
Decision-making around thrombopro-phylaxis	***Now I'd like to ask you some questions about evaluating transgender adolescents and young adults for thrombosis risk and potentially prescribing thromboprophylaxis. I'll be asking separate questions about recommending and prescribing thromboprophylaxis because sometimes these are different behaviors for some physicians.*** 23. How do you feel about the idea of recommending thromboprophylaxis to a transgender adolescent who is at higher risk of thrombosis and wants to start estrogen for gender-affirming hormonal therapy? - Do you feel differently about the idea of actually prescribing thromboprophylaxis in this case? - Would you feel differently if we were talking about a young adult patient age 18 or older? - Would you feel differently if we were talking about someone who wants to start testosterone? 24. Which transgender youth ages 13-17 years would you consider at increased risk for thrombosis? - Does this determination change based on whether someone is starting estrogen vs. testosterone therapy? Or by age: under 18 years vs. 18 years or older? 25. What laboratory evaluation would you recommend? - Would your evaluation change based on whether the youth was starting estrogen vs. testosterone therapy? 26. What personal or family risk factors would lead to recommending thromboprophylaxis? What laboratory results? - Would this differ by age group for those under 18 vs. 18 years or older? - Would this differ by estrogen vs. testosterone therapy? 27. What medication would you recommend for thromboprophylaxis for youth at higher risk of thrombosis on estrogen for gender-affirming hormone therapy? Dose? How long would you intend use of this medication? - Would your recommendation change if the person were starting testosterone? If so, what would be different? 28. Are there any situations in which a patient might have a risk factor for thrombosis, but you would NOT recommend thromboprophylaxis?

	29. Are there any situations in which you would recommend against starting estrogen for gender-affirming hormone therapy due to thrombosis risk? If so, which situations? - Would this differ by age (adolescent vs. young adult?) 30. Are there any situations in which you would recommend against starting testosterone for gender-affirming hormone therapy due to thrombosis risk? If so, which situations? - Would this differ by age (adolescent vs. young adult)? 31. Would there be any patients to whom you would feel more comfortable recommending or prescribing thromboprophylaxis?
Sharing of current data about thrombosis risk in the setting of gender-affirming hormone therapy	***Thank you for sharing your thoughts with me so far. I'd like to take some time to share with you the current research to date about thrombosis risk for people using gender-affirming hormone therapy in order to learn from you whether this might change your responses to some of the questions we just discussed.*** (The following information will be provided both verbally and in written form.) The only study to date that examined the risk of thrombosis and prevalence of risk factors for thrombosis specifically among transgender adolescents and young adults in the setting of gender-affirming hormone therapy was conducted by our group. In a retrospective chart review of 611 transgender youth with median age of 17 years, nearly 30% of whom identified as transgender women, there were no incidents of thrombosis. In terms of risk factors for thrombosis, 59% of youth were overweight or obese, 15% were smokers, 5% reported migraine with aura, and 8% had a family history of thrombosis. (Mullins, *Pediatrics*, 2021) The remaining data about thrombosis risk in the setting of gender-affirming hormone therapy is from studies of adults. 1) Among 4960 transgender adults, 57% of whom were transgender women, there was an increased incidence of venous thromboembolism in transgender women as compared to both cisgender women and cisgender men, and the incidence of thromboembolism increased with longer duration of follow up (and thus hormone use). Incidence of myocardial infarction was also higher in transgender women compared to cisgender women. There was no increase in acute cardiovascular events in transgender men. (Getahun, *Annals of Internal Medicine*, 2018) 2) In a European study of transgender adults with mean duration of hormone use of 7.7 years (transgender women) and 9.4 years (transgender men), 5.1% (n=11) of transgender women developed venous thromboembolism or pulmonary embolism during treatment; half of these occurred in the first year of hormone treatment. Ten of these women had other risk factors for thromboembolism, such as smoking, immobilization, and/or clotting disorder. There were no events in transgender men. (Wierckx, *European Journal of Endocrinology*, 2013) 3) In study from the Netherlands of transgender adults, a subset of coagulation factors was measured at baseline and 12 months after starting gender-affirming hormone therapy. Adherence and hormone levels were not included in the manuscript. (Scheres, *Journal of Thrombosis and Hemostasis*, 2021) a) Transgender women: Mean age 33.7 years; 93% of participants on estrogen hormone therapy were also taking an anti-androgen that is not approved in the U.S. (cyproterone acetate), which has not been studied in relation to coagulation factors and thus may confound the findings.

Procoagulant Changes	Anticoagulant changes
↑ Factor IX (+9.6 IU/dL)	↑ APC ratio (+ 0.15)
↑ Factor XI (+13.5 IU/dL)	↓ Hematocrit (-3%)
↓ Protein C (-7.7 IU/dL)	↑ Free protein S (+2.5 IU/dL)
↑ Fibrinogen (+ 10 mg/dL)	

b) Transgender men: Mean age 26.9 years.

Procoagulant Changes	Anticoagulant changes
↑ Factor IX (+7.9 IU/dL)	↑ APC ratio (+ 0.48)
↑ Hematocrit (+6%)	↓ FII (-5.7 IU/dL)
	↑ Free protein S (+7.6 IU/dL)
	↓ Factor XI (-7.7 IU/dL)

After learning about these studies:
a) Does this impact your thoughts about to which transgender women you might recommend thromboprophylaxis?

b) Does this impact your thoughts about to which transgender men you might recommend thromboprophylaxis?

Theory-based Predictors: Theory of Planned Behavior (TPB)	32. With your current knowledge, what are some benefits of gender-affirming hormone therapy? What are some risks? 33. What are some benefits that might result from your recommending and/or prescribing thromboprophylaxis to transgender youth at increased risk of thrombosis? 34. Who, and what organizations, would be influential in motivating you to recommend and/or prescribe thromboprophylaxis to transgender youth? 35. If official recommendations from such an organization were released supporting the use of thromboprophylaxis for transgender youth at increased risk for thrombosis, how would that impact your comfort with recommending/prescribing prophylaxis? 36. If official recommendations from such an organization were released supporting the use of thromboprophylaxis for adolescent outpatients, how would that impact your comfort with recommending/prescribing prophylaxis? 37. What factors would help or facilitate your recommendation and/or prescribing thromboprophylaxis to transgender youth at increased risk of thrombosis who are starting gender-affirming hormone therapy? 38. What factors would be barriers to your recommending and/or prescribing thromboprophylaxis to transgender youth at increased risk of thrombosis who are starting gender-affirming hormone therapy? (***Probe*:** patient-related barriers (i.e. cost, not wanting to take another medication,

	concerns about adverse events, parental reluctance); provider barriers, including off-label use of medications for this indication) 39. What information or training would you need to feel comfortable recommending/prescribing thromboprophylaxis to transgender youth starting gender-affirming hormone therapy who are at increased risk of thrombosis? How should such information be delivered?
Structural/Policy Factors	40. How might coverage by insurance impact your willingness to prescribe thromboprophylaxis to transgender youth? 41. How might an FDA-indication supporting use of medications for thromboprophylaxis for outpatient pediatric patients impact your willingness to prescribe prophylaxis to a transgender youth on gender-affirming hormone therapy at higher risk of thrombosis?
Intentions toward use of thrombopro-phylaxis for transgender youth at higher risk of thrombosis	***I'd like to wrap up our interview by asking about your intentions to recommend or prescribe thromboprophylaxis to transgender youth starting gender-affirming hormone therapy who are at increased risk for thrombosis. For these questions, "adolescents" are ages 13-17 years, and "young adults" are youth age 18-22 years.*** 42. How likely are you to recommend thromboprophylaxis to a transgender adolescent who is at higher risk of thrombosis and starting estrogen for gender-affirming hormone therapy? 43. How likely are you to recommend thromboprophylaxis to a transgender adolescent who is at higher risk of thrombosis and starting testosterone for gender-affirming hormone therapy? 44. How likely are you to prescribe thromboprophylaxis to a transgender adolescent who is at higher risk of thrombosis and starting estrogen for gender-affirming hormone therapy? 45. How likely are you to prescribe thromboprophylaxis to a transgender adolescent who is at higher risk of thrombosis and starting testosterone for gender-affirming hormone therapy? 46. How likely are you to recommend thromboprophylaxis to a transgender young adult who is at higher risk of thrombosis and starting estrogen for gender-affirming hormone therapy? 47. How likely are you to recommend thromboprophylaxis to a transgender young adult who is at higher risk of thrombosis and starting testosterone for gender-affirming hormone therapy? 48. How likely are you to prescribe thromboprophylaxis to a transgender young adult who is at higher risk of thrombosis and starting estrogen for gender-affirming hormone therapy? 49. How likely are you to prescribe thromboprophylaxis to a transgender young adult who is at higher risk of thrombosis and starting testosterone for gender-affirming hormone therapy?
Close	***Thank you for sharing your thoughts with me and for taking time to participate in this study. Are there any other thoughts that you'd like to share before we complete the interview?***