National Institute of Environmental Health Sciences (NIEHS)

Report Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities in Clinical Research as Reported in FY2019 – FY2021

I. Background/Overview

Among the 27 research institutes and centers that comprise the National Institutes of Health (NIH), the National Institute of Environmental Health Sciences (NIEHS) is the institute most focused on prevention rather than diagnosis or treatment of health issues. The mission of the National Institute of Environmental Health Sciences is to discover how the environment affects people in order to promote healthier lives. Our vision is to provide global leadership for innovative research that improves public health by preventing disease and disability.

The NIEHS research agenda is based on the concept that all complex diseases have both an environmental and a genetic component, and the Institute focuses on understanding the environmental component and the interaction of environment with genetics. Research programs cover the effects of environmental exposures throughout the lifespan, from preconception to old age. Funded studies range from computational and cell-based models to epidemiological studies with human subjects. The more we know about environmental exposures and how they affect health outcomes, the greater our ability to create healthy environments by reducing or preventing hazardous exposures. To this end, NIEHS investments are significant and measurable.

The Extramural Division includes review, grants management, program analysis and five program branches with focus on different aspects of the grant portfolio. DERT staff plans, reviews, approves, directs, fiscally administers, and evaluates performance of the Institute's grant, cooperative agreement, and contract programs, all of which support research and training in environmental health science. In addition, the extramural review staff review the research contracts that support the intramural human studies.

The Intramural Division conducts a broad range of human studies primarily through research contracts. In addition, NIEHS has an on-site Clinical Research Program with the primary goals of translating basic laboratory findings to humans; studying interactions between genetic susceptibility (host factors) and environmental

factors in the pathogenesis of complex human traits and diseases; and identifying populations at increased risk and developing novel preventative and therapeutic strategies to combat human diseases. NIEHS also has a clinical program on autoimmune diseases, in particular myositis, at the NIH Clinical Center in Bethesda, Maryland.

II. Strategies for Ensuring Compliance

Peer Review

The implementation of inclusion guidelines involves the participation of review, program, policy, and grants management staff. Inclusion is first addressed by peer review. Reviewers on NIH peer review panels are given specific guidance on reviewing inclusion on the basis of sex/gender, race, ethnicity, and age when considering clinical research applications.

Reviewers evaluate applications for the appropriateness of the proposed plan for inclusion by sex/gender, race, and ethnicity. For NIH-defined Phase III clinical trials, enrollment goals are further assessed for plans to conduct analyses of intervention effects among sex/gender, racial, and ethnic groups. Unacceptable inclusion plans must be reflected in the priority score of the application and documented in the minutes of the review session. Initial review groups make recommendations as to the acceptability of the proposed study population with respect to the inclusion policies. If issues are raised in review, program staff notify principal investigators, who are required to address these issues prior to funding.

The NIEHS Advisory Council performs the second level of review and makes recommendations for funding to the NIEHS Director considering the overall impact score, percentile ranking, and summary statement in light of the research priorities for NIEHS. Applications with unacceptable inclusion plans receive a bar to funding, and an award is not issued until an acceptable resolution is received. If the award is to be made at the end of the fiscal year and there is insufficient time to resolve the bar, the award is issued with a restriction on the use of human subjects until the resolution is received and the restriction removed.

Program Monitoring and Grants Management Oversight

Prior to an award, an inclusion specialist reviews the inclusion information in the application and makes recommendations to the program officer who determines whether the plans are scientifically appropriate. Program staff monitor enrollment through the annual progress reports. The inclusion specialist is consulted when needed. For NIH-defined Phase III clinical trials, program officials/program directors monitor the study to ensure they meet the additional requirements, including the reporting of sex/gender and race/ethnicity analyses in applications and annual progress reports when needed. Grants management staff ensure that appropriate terms and conditions of award are included in the Notice of Award, and that this information is appropriately documented in the official grant file.

Intramural

All intramural clinical research studies require investigators to provide plans for the appropriate inclusion of women and minorities and/or a justification whenever representation is limited or absent. These plans are considered during the scientific review process. With the annual scientific review and IRB review renewal, the investigator documents the number, sex/gender, race and ethnicity of those who were accrued during the past year; any issues with accrual are addressed and plan to increase recruitment reviewed by both the Institute and the pertinent IRB. The Clinical Center's Office of Protocol Services (OPS) coordinates annual reporting of demographic participant data to the Office of Extramural Research (OER) and the Office of Research on Women's Health. On the rare occasion that an intramurally funded trial is not reviewed by one of the NIH IRBs, the extramural inclusion specialist enters the study record, including the enrollment and age data, which is provided by the project officer.

IC Training Approaches

Over the past three years, staff have taken a number of trainings related to inclusion and other human subjects related policies. Institute Program Officials/Program Directors and Scientific Review Officers attended the "2020 Inclusion Training for Program Staff" and the "2020 Inclusion Training for Review Staff" in April 2020; "Human Subjects Research - Revised HHS Regulations and NIH Implementation" in July 2020; "Using HSS and Other eRA Systems for Monitoring Human Subjects Research" in December 2020; and "Secondary Research and Inclusion Policies" (on demand taped

training). Additional human subjects related training options attended by staff include "The Dickey-Wicker Amendment and NIH Human Embryo Research Policy" in September 2021; "Harmonizing NIH Institutes and Centers Clinical Trial Standard Operating Procedures Webinar and Q&A" in July 2021; "Resources for Basic Experimental Studies involving Humans (BESH): and Preview of resources and refresher for staff" in April 2021. Good Clinical Practice new or refresher, training was completed by all staff required to take the course. In addition, the DERT inclusion specialist gave trainings to staff on "Monitoring Inclusion in Progress Reports" and on the "Human Subjects System" and is available to staff to answer human subjects' inclusion, clinical trial and systems related questions. The NIH Office of Human Subjects Research Protections (OHSRP) provides a monthly training series for Intramural staff who work with human subjects.

Compliance

To ensure compliance with policies, the DERT Inclusion specialist is responsible for reviewing a minimum of 20% of the grants for accuracy of data annually. This process includes notifying the program officer when issues are found, suggesting corrections and requesting revisions from principal investigators when necessary. In addition, the specialist performs reconciliation of the data at year's end. She also maintains the Good Clinical Practice Training records, reminding staff when it is time for refresher training and recording completion.

III. Analysis and Interpretation of Data

Tables of NIEHS inclusion data covering the three-year period of this report are provided in the appendix. All data tables include combined extramural, intramural and contract data for fiscal years (FY) 2019-2022. The tables are provided by NIH.

As shown in Table 2-1, the number of Inclusion Enrollment Records (IERs) varies over the three year period, increasing by 5.1% between 2019 and 2020 and decreasing by 1.6% in 2021. While it may fluctuate somewhat over the three years, the majority of the IERs (78-82%) are enrolling from US sites. Foreign countries in which NIEHS supported research have taken place during the past three years include Mexico, the Faroe Islands, China, Bangladesh, Ecuador, Uruguay, South Africa, Nigeria, and Kenya.

For single sex studies, it is important to note that, as many of our studies include mother or caregiver (which is usually, but not always, the mother) /child pairs for recruiting studies, the NIEHS Extramural Division reports adults separately from children. Reporting adults separately from children ensures staff knows the number of adults who have been recruited are adult women/men or girls/boys. For this reason, a significant percentage of the IERs are female only. The male only studies include research of environmental factors on male reproductive development or fertility.

Table 5-1-1-c displays the total number of participants enrolled by year and sex/gender in all prospective studies funded by the Institute. There were 14.1% fewer participants reported between 2019 and 2020 with another 3.1% fewer enrolled between 2020 and 2021. Seven studies that ended in 2019 accounted for approximately 64% of the reduction. No studies with large numbers of participants ended in 2020. While the number of females increased from 75.4% in 2019 to 79.5% in 2020 with a slight drop to 79.2% in 2021, the number of minority women decreased from 23.4% in 2019 to 18.3% in 2021. Overall male enrolled decreased from 23.2% to 19.8% between 2019 and 2020 and increased slightly to 20.1% in 2021. At the same time male minority participation rates fluctuated over the three years from 40% in 2019 to 44% in 2020 and 32.9% in 2021. Overall, the rates for failure to identify gender over the three year period decreased from 1.3% to 0.7%. Minority failure to identify gender fell from 34.4% to 4.6% over the same timeframe. The minority data includes those who identify as American Indian/Alaska Natives, Asian, Black/African American, Native Hawaiian/Pacific Islander, More than one race, White Hispanics and those that identify as Hispanic unknown race.

Ethnicity and Race Data

Between 2019 and 2021, the number of people identifying as Not Hispanic rose from 87.3% to 91.1%, while the percentage of participants identifying as Hispanic fell from 9.7% in 2019 to 9.3% in 2021. The percentage of people whose ethnicity is unknown decreased from 3.1% to 1.5% between 2019 and 2020 and rose slightly between 2020 and 2021 to 1.6%. For race, the data shows rates of participation between 2019 and 2021 dropped from 1.3% to 0.7 % for persons identifying as American Indian/Alaska Natives; decreased from 3.5% to 2.2% with 2020 being somewhat higher at 4.6% for those identifying as Asian; dropped from 11.8% to 10% for persons identifying as Black/African American; increased steadily from 75% to 81.1% for persons identifying as White; and dropped from 2.7 % to 1.9% for those identifying as

More than one race. The rate of failure to identify race decreased from 5.6% to 3.9%, which is a 31% improvement over the three years.

NIEHS recognizes the importance of diversity in human subjects' research. As part of the strategy to increase diversity, staff have created programs in community-based research, research to action, and have added community outreach and education to multi-project grants. These strategies have been shown to be effective. However, transition to the Human Subjects System was difficult and there are significant anomalies in the data, particularly for 2019. Therefore, it isn't known whether these differences are real or an artifact of the difficulties with the transition.

Table 5-2-2-C shows the accrual of participants of all Phase III clinical trials supported by NIEHS. NIEHS rarely funds Phase III trials with none supported in 2019 or 2020. So, this table includes the enrollment of participants in the sole Phase III clinical trial supported with NIEHS funds, which was awarded in 2021. This is a random controlled trial of exercise on per- and polyfluoroalkyl substances (PFAS) in obese pregnant sedentary women in Arkansas and the development of their infants to age 2. While this is a small NIH-defined Phase III trial, it is not considered to be an applicable clinical trial under 42 CFR Part 11 and does not require reporting of valid analysis in clinical trials.gov. However, the PI does plan to do all race/ethnicity and sex gender analyses where applicable.

Table 1 shows the participants in NIEHS enrolling studies by narrow age groups: ages from newborns through age 17 are children; ages 18-64 are adults; and anyone 65 or over is considered an older adult. This initial snapshot of the NIEHS combined portfolio of Intramural and Extramural research, is comprised of 16.9% children, 68.5% adults, and 14% older adults. A small percentage (0.7%) did not report age. It will be of interest to see how, or whether, this changes at the next reporting period.

Chart A-1 displays the age data in a visual format using narrow age groups. Due to privacy rules, in the narrow age categories, participants aged 90 and over are reported as one group. While the majority (62.9%) of participants range in age between 26-59, NIEHS supported research does include a significant number (8.8%) of older adults age 65-69, children (7.3%) age 6-12, and infants (4%) less than one year old. While the numbers are much smaller in the older age ranges, 2.9% fall between ages 70-89 and 0.1% are 90 or older, it is encouraging that we do see people in these range groups represented in our supported research.

Research, Condition, and Disease Categorization (RCDC)

Recognizing the importance of keeping the American people informed about how their tax dollars are spent to support medical research, in January 2009, the NIH added the Research, Condition, and Disease Categorization (RCDC) reports to the RePORT site. RCDC is a computerized process the NIH uses to categorize and report the amount it funded in each of the more than 280 reported categories of disease, condition, or research area. As of January 2019, as part of the RCDC reporting, the data now also can be viewed by the NIH Inclusion of Women and Minorities categories of Gender/Race/Ethnicity /(https://report.nih.gov/RISR/#/). Using the dropdown boxes at the top, the data can be viewed for all of NIH or broken out by the individual Institutes. RCDC has created new tables with age data that will be available in March 2022.

Please note that the inclusion categories are not mutually exclusive, so the same projects may appear in more than one category. All participants enrolled in a project's studies are included in all categories associated with that project. Individual research projects can be included in multiple categories so amounts depicted within each column of this table do not add up to the total participants enrolled in NIH-funded research.

Explanation of Differences from Previous Years

NIH transitioned from the Inclusion Management System to the Human Subjects System (HSS) in July 2018. The new system is significantly different, and more complex, than previous iterations. The original systems included only planned/cumulative inclusion enrollment records (IERs), whereas the HSS is comprised of study records within which the IERs are embedded. So instead of a one-to-one relationship between study and IER, there is a study record which can include up to 20 IERs. Thus, reviewing data takes more steps. For example, if you look at the NIH view of the study records in the HSS, you will see a list of one or more study records in a table with the summary of the total planned and cumulative enrollment for each study. A study record summary may display 1,000 in planned and 4,000 in cumulative. Looking just at this summary, one could think enrollment is concluded and 3,000 more participants have been enrolled than were planned. It isn't until the study record is opened that one can see three IERs and that the 4,000 cumulative is actually comprised of two IERs that are using existing data, while enrollment has not begun for the study

that is planned to enroll. Thus, reviewing the details is necessary to understand what has been accomplished and ensure accuracy.

While we know the data will never be perfect, we know the 2019 data is particularly problematic. There was a lot of initial confusion by both staff and grantees with the new system, and the effects of some changes were not immediately recognized. Initially, many grantees created new study records or inclusion enrollment records instead of updating the original records, which resulted in duplicate studies and/or IERs that often went unrecognized by staff. Over time, duplicates have been removed.

Around the same time, changes in the Common Rule and NIH policy on acceptance of the IRB determination resulted in studies that were originally reported by the PI in the application as non-exempt human subjects research or fell under exemption 4 but were reported differently in the first progress report resulting in changes to the grant coding. While we accept the IRB determination, when there is a question of whether what was submitted in the application Is consistent with the IRB determination, we now ask what the actual determination is so the grant coding is accurate from the start.

In 2020, NIH instructed we remove unfunded supplements after it was recognized that when they remained in the system their data was included in the dataset. It also has taken time, experience with the system and additional training for inclusion staff to learn to identify and correct records that appear fine but have internal inconsistencies that affect data reporting.

We also know that Sar-CoV-2 affected recruitment in 2020 that continued into 2021 and, possibly, further. Initially, the virus stopped virtually all research for 6 months or so as lockdowns designed to decrease transmission prevented many studies from moving forward. Some studies were modified to do remote data collection, which may have contributed to the decline in participation by under-represented minorities, particularly in rural and poor communities that lack access to the internet. Some studies were paused until they had the supplies and space to do in person data collection safely, and we had one study where the IRB required the investigator to release their participants and begin again.

Thus, these factors, combined with the natural fluctuation as grants end and new grants begin, explain the unusual differences seen over the previous years. However,

many of these issues have been resolved and, barring unforeseen events, we anticipate reliability of reporting to continue to improve.

IV. Additional information

The 21st Century Cures Act, enacted December 13, 2016, included several new requirements related to inclusion of participants in clinical research. As a result, NIH updated its policy on the Inclusion of Women and Minorities as Subjects in Clinical Research on November 28, 2017, to require studies that are both NIH-defined Phase III clinical trials and applicable clinical trials to report the results of analyses by sex/gender and/or race/ethnicity to ClinicalTrials.gov. This requirement is effective for competing grant awards on or after December 13, 2017, as well as contract solicitations and intramural studies initiated after this date.

Additionally, NIH revised its Inclusion of Children Policy on December 19, 2017. The revised policy, now called the NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects, applies to individuals of all ages and requires reporting of participant age at enrollment in annual progress reports. The policy was effective for grant applications submitted on or after January 25, 2019, as well as contract solicitations and intramural studies initiated after this date.

The 21st Century Cures Act also amended the frequency of the Report of the NIH Director on the inclusion of women and minorities from biennial to triennial. This is the second triennial report which provides information on inclusion of participants in NIH clinical research from FY 2019 – 2021.

Appendix

Section 2: Metrics Based on Inclusion Enrollment Records (IERs)

Table 2-1. Total Inclusion Enrollment Records (IERs) for NIH-Defined Extramural and Intramural Clinical Research Reported Between Fiscal Years 2019 and 2021

	Total IERs	IERs Without Enrollment	IERs With Enrollment	US Site IERs	Non-US Site IERs	Female Only IERs	Male Only IERs	IERs Excluding Male only and Female only*
2019	490	145	345	281	64	86	12	247
2020	515	220	295	231	64	78	8	209
2021	507	222	285	235	50	70	7	208

*Inclusion Enrollment Records (IERs) excluding male only and female only include unknown sex/gender, and combination of unknown and any sex/gender(s).

Total Enrollment: All NIH-Defined Clinical Research

Table 5-1-1-C. Enrollment for All NIH-Defined Clinical Research, Sex/Gender by Race and Ethnicity

Fiscal Year	Sex Gender	Minority	% Minority	Total Enrollment	% Total	Not Hispanic	% Not Hispanic	Hispanic Latino	% Hispanic Latino	Unknown Not Reported	% Unknown Not Reported
2019	Female	72,664	23.4	310,939	75.4	281,285	90.5	24,559	7.9	5,095	1.6
2019	Male	38,295	40.0	95,742	23.2	76,260	79.7	15,074	15.7	4,408	4.6
2019	Unknown	1,909	34.4	5,555	1.3	2,137	38.5	259	4.7	3,159	56.9
2020	Female	61,492	21.8	281,454	79.5	256,781	91.2	22,420	8.0	2,253	0.8
2020	Male	30,846	44.0	70,089	19.8	57,740	82.4	11,052	15.8	1,297	1.9
2020	Unknown	556	20.7	2,687	0.8	838	31.2	111	4.1	1,738	64.7
2021	Female	49,813	18.3	271,834	79.2	251,395	92.5	18,019	6.6	2,420	0.9
2021	Male	22,713	32.9	69,045	20.1	60,472	87.6	7,032	10.2	1,541	2.2
2021	Unknown	114	4.6	2,470	0.7	839	34.0	64	2.6	1,567	63.4

Fiscal Year	Sex Gender	American Indian Alaska Native	% American Indian Alaska Native	Asian	% Asian	Black African American	% Black African American	Native Hawaiian Pacific Islander	% Native Hawaiian Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown Not Reported	% Unknown Not Reported
2019	Female	2,846	0.9	8,920	2.9	33,195	10.7	334	0.1	246,788	79.4	7,623	2.5	11,233	3.6
2019	Male	2,412	2.5	5,596	5.8	13,826	14.4	122	0.1	61,852	64.6	3,269	3.4	8,665	9.1
2019	Unknown	20	0.4	65	1.2	1,549	27.9	4	0.1	637	11.5	89	1.6	3,191	57.4
2020	Female	1,788	0.6	10,052	3.6	25,171	8.9	303	0.1	229,732	81.6	5,548	2.0	8,860	3.1
2020	Male	1,295	1.8	5,935	8.5	11,529	16.4	93	0.1	42,697	60.9	2,463	3.5	6,077	8.7
2020	Unknown	2	0.1	333	12.4	73	2.7	0	0.0	820	30.5	47	1.7	1,412	52.5
2021	Female	1,398	0.5	5,107	1.9	23,196	8.5	300	0.1	229,910	84.6	4,896	1.8	7,027	2.6
2021	Male	976	1.4	2,490	3.6	11,259	16.3	91	0.1	47,710	69.1	1,656	2.4	4,863	7.0
2021	Unknown	13	0.5	11	0.4	21	0.9	0	0.0	797	32.3	12	0.5	1,616	65.4

The data presented in this report show only inclusion data records labeled as prospective data. Inclusion data records labeled as existing data are excluded.

All Enrollment: All NIH-Defined Clinical Research

Table 5-2-2-C. ALL Enrollment for NIH-Defined Extramural and Intramural Phase III Clinical Research, Sex/Gender by Race and Ethnicity

Fiscal Year	Sex Gender	Minority	% Minority	Total Enrollment	% Total	Not Hispanic	% Not Hispanic	Hispanic Latino	% Hispanic Latino	Unknown Not Reported	% Unknown Not Reported
2019	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2019	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2019	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2020	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2020	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2020	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2021	Female	129	42.9	301	77.0	289	96.0	12	4.0	0	0.0
2021	Male	41	45.6	90	23.0	84	93.3	6	6.7	0	0.0
2021	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

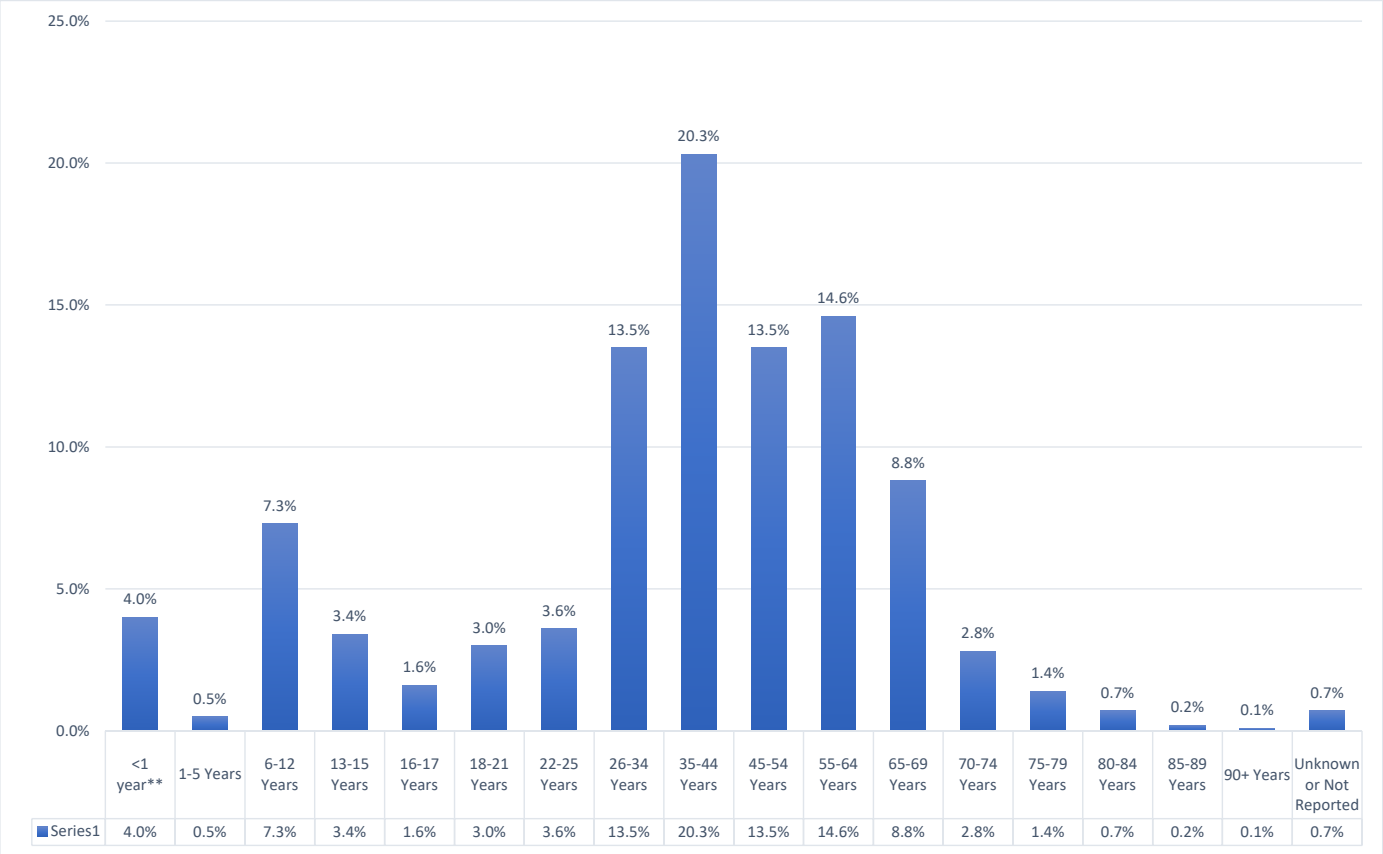
Fiscal Year	Sex Gender	American Indian Alaska Native	% American Indian Alaska Native	Asian	% Asian	Black African American	% Black African American	Native Hawaiian Pacific Islander	% Native Hawaiian Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown Not Reported	% Unknown Not Reported
2019	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2019	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2019	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2020	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2020	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2020	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2021	Female	1	0.3	1	0.3	109	36.2	0	0.0	181	60.1	7	2.3	2	0.7
2021	Male	0	0.0	0	0.0	32	35.6	0	0.0	54	60.0	3	3.3	1	1.1
2021	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Age Data Based on Inclusion Data Records (IERs)

Table 1. Age Distribution Using Broad Age Groups for NIH-Defined Extramural and Intramural Clinical Research Reported for Fiscal Year 2021.

Fiscal Year	Children (<18 years)	Adults (18-64 years)	Older Adults (65+ years)	Unknown or Not Reported	Total
2021	2,693	10,945	2,237	104	15,979
	16.9%	68.5%	14.0%	0.7%	100%

Chart A-1: NIH Clinical Research Enrollment by Narrow Age Groups



**Includes all ages equivalent to less than one year, including all those reported in days, weeks, months, and years