NIH Policy on the Inclusion of Children in Clinical Research:

Evaluation of Policy Implementation at the NICHD

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Evaluation Report Highlights:
The NIH Policy on the Inclusion of Children in Clinical Research

The Policy

Biomedical and behavioral research is needed to identify the best prevention and treatment interventions specifically for children. Because the course of conditions and response to treatment often differ in children and adults, researchers must include children in clinical research, and analyze data related specifically to children. In 1998, the NIH implemented a policy to ensure the appropriate inclusion of children in biomedical research. The NIH policy requires that scientists applying to NIH for support for clinical research projects include children in their studies, unless there are valid scientific and/or ethical reasons not to include children.

The Evaluation Findings

The NICHD conducted a program evaluation to assess how frequently children under 21, and children under 18, were included in research grants supported by the NICHD; how frequently investigators planned to analyze data by the age of the participants; NICHD researchers' stated reasons for not including children; and how study sections implemented the NIH policy for NICHD grants. The study reviewed data from NICHD-funded grants for FY 2007 with human subjects.

The evaluation found that:

1. 87 % of grants included children under age 21, while 13 % included only people over age 21.
2. 65 % of grants included children under age 18, while 35 % included only people over age 18.
3. When children were excluded, the most common reasons given were that a) the research did not apply to children, or b) a separate study was preferable.
4. Neither reviewers nor applicants consistently defined adulthood as age 21 and older.
5. Of grants that included children under age 21, half planned to analyze data by age.
6. About 1 % of grant applications were rated unacceptable by study sections for reasons related to the inclusion of children.
7. Research mechanism and subject matter were associated with the inclusion and exclusion of children, the analysis of data by age, and "unacceptable" ratings by the study section.

This program evaluation was conducted by a team comprised of staff from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), MasiMax Resources Inc., and The Madrillon Group Inc., under the direction of the Office of Science Policy, Analysis and Communication, NICHD. Funding for the evaluation was provided through the Evaluation Branch, Office of the Director, National Institutes of Health, from the Department of Health and Human Services Evaluation Set-Aside program.

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Introduction

Children can suffer from many of the same health conditions that affect adults, including diabetes, cancer, and infectious diseases. However, although the conditions may be the same, children may experience a different course of disease than adults, and they will often require specialized dosing or treatment. Because children are different from adults – physiologically, developmentally, and behaviorally – it is usually not appropriate to extrapolate data from studies on adults and assume that the same data can be applied to children. Biomedical and behavioral researchers must include children in clinical research studies to identify the correct prevention, diagnosis and treatment interventions specifically for children. The U.S. National Institutes of Health (NIH), the largest funding agency for biomedical research in the world, implemented a special policy in 1998 to ensure the appropriate inclusion of children in biomedical research. The NIH policy required that scientists applying to the NIH for clinical research projects include children in their studies, unless there are valid scientific and/or ethical reasons not to include them.

At the request of the American Academy of Pediatrics, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) conducted a program evaluation study of the implementation of the NIH pediatric inclusion policy, as applied to grants funded by the NICHD in FY 2007. The purpose of the study was to assess how frequently researchers planned to include children in NICHD-funded grants; how frequently NICHD scientists planned to analyze data by the age of the subjects; NICHD researchers' reasons for excluding children from research; and how study sections implemented the NIH policy for NICHD grants. This report describes the results of the study.

The NIH Policies on the Inclusion of Women, Minorities, and Children in Research

The History of the NIH Policies

In one of the earliest clinical research experiments in Europe, in 1798 Dr. Edward Jenner deliberately infected a healthy patient with cowpox, then exposed the patient to the more deadly disease smallpox, to demonstrate that this procedure he called "vaccination" could protect against smallpox. The subject in this potentially dangerous clinical experiment was a 10 year old boy.[1]

[1] Davies, Hugh. 2007. "Ethical Reflections on Edward Jenner's Experimental Treatment", Journal of Medical Ethics, 33, 174-176.

Throughout much of the twentieth century, however, biomedical research studies were conducted largely with adult subjects, and it was simply assumed that the results of research on adults also applied to children. When children were involved in research, often the subjects were foundlings, orphans, or other institutionalized children. Several well-publicized cases where research subjects were abused, such as the Tuskegee experiments, raised serious concerns about the protection of research subjects. Many of the most egregious cases involved subjects who were thought to be especially vulnerable to exploitation. Women, minorities, and children in particular were thought to need special protections against questionable research practices. As a result, when government agencies developed and expanded formal regulations for the protection of human subjects in the 1970s, extra measures were urged to protect women, minorities and children.

After years of these extra cautions, however, it became apparent that these supposedly vulnerable populations may have been protected to their own detriment. The HIV/AIDS epidemic particularly affected minorities, and AIDS advocates and patients demanded the earlier access to experimental therapies that came with participation in clinical trials. Moreover, it became increasingly apparent that women responded to both disease and treatment differently from men. Similarly, children and even adolescents were no longer viewed as "little adults"; it was clear that children differed from older populations in how they were affected by both treatments and the underlying conditions.[2] Consequently, extrapolating data from studies of adult men and assuming these data would apply to women and children did not serve them well. The women's health movement soon insisted that women be included in clinical research, and pediatricians and child advocates strongly supported greater inclusion for children as well. The prevailing philosophy began to shift from protecting individual subjects, especially vulnerable populations, to facilitating their participation in order to ensure that all groups benefit equally from biomedical research.[3] The NIH, reflecting this change, implemented policies on the inclusion of women and minorities in research. Subsequently, the NIH implemented a formal policy on the inclusion of children in research. Table 1 shows a timeline of events leading up to the establishment of the NIH policies on inclusion of women, minorities, and children. Each of the different policies provides an important context for the others, especially in their similarities and differences.

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[2] Institute of Medicine, 2004. The Ethical Conduct of Clinical Research Involving Children, National Academy of Sciences Press.

[3] Taylor, Holly A. 2009. "Inclusion of Women, Minorities and Children in Clinical Trials: Opinions of Research Ethics Board Administrators", Journal of Empirical Research on Human Research Ethics, 4, 65-73.

Table 1: Timeline of Key Events in the Development of NIH Policies

Year	Event
1972	Reports of subject exploitation in Tuskegee study were widely publicized
1973	HHS regulations on protection of human subjects were established
1985	NIH Advisory Committee on Women's Health recommended that women be more widely included in clinical research
1987	First NIH policy statements were issued about the inclusion of women and minorities in clinical research
1990	U.S. General Accounting Office reported on NIH implementation of inclusion policy statements
1993	NIH Revitalization Act mandated inclusion of women and minorities in research
1994	NIH published its formal policy on inclusion of women and minorities in research
1994	The American Academy of Pediatrics asked NIH to develop a new policy on the inclusion of children in clinical research
1995-1996	NIH and AAP held a workshop and expert panel meeting on issues related to the inclusion of children in research
1998	NIH implemented its formal policy on inclusion of children in research

NIH Policies on Inclusion of Women and Minorities in Clinical Research

In 1985, the NIH Women's Advisory Committee recommended that all NIH applicants include women in their clinical research, or justify their exclusion. The NIH followed up by issuing policy statements supporting the inclusion of women and minorities in research. However, in 1990 the U.S. General Accounting Office, the investigative and research arm of the U.S. Congress, reported that the NIH had made little progress in implementing these recommendations.[4] To ensure vigorous implementation of these policies, the Congress incorporated them into law through the NIH Revitalization Act of 1993 (P.L. 103-43). The NIH released formal guidelines mandating inclusion of women and minorities in clinical research. These guidelines were first issued in 1994, and then revised in 2001.

The NIH Guidelines on the Inclusion of Women and Minorities in Clinical Research require that for all NIH-supported clinical research studies, women and members of minority groups must be included, unless a

[4] U.S. General Accounting Office. 1990. National Institutes of Health: Problems in Implementing Policy On Women in Study Populations, testimony to the Select Committee on Aging, United States Senate, July 24, 1990. GAO/T-HRD-90-50.

clear and compelling rationale establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.[5] Cost is not an acceptable reason for exclusion, except in cases where the study would duplicate data from other sources.

For NIH-defined phase III clinical trials, the policy requirements are more stringent.[6] For phase III clinical trials, the investigator must review the evidence to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected.

- If prior studies support the existence of significant differences, the researcher is required to ensure that the primary question(s) to be addressed by the proposed clinical trial accommodate such differences. For example, if men and women are thought to respond differently to an intervention, then the Phase III clinical trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each. The proposal must include an analysis plan specifically for detecting these differences in responses.
- If prior studies support no significant differences in intervention effect based on sex/gender or racial/ethnic comparisons, then sex/gender and race/ethnicity will not be required as subject selection criteria, although the inclusion of all subgroups is strongly encouraged.
- If prior studies neither support nor negate significant differences, the investigator will be required to include sufficient and appropriate entry to sex/gender and race/ethnicity participants so that valid analyses of the intervention effects can be performed.[7] Moreover, the research plan must include a

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[5] U.S. Department of Health and Human Services, National Institutes of Health. The NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research—Amended, October 2001. http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

[6] For the purpose of these guidelines, an NIH-defined clinical trial is a broadly-based, prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparisons with a standard or control intervention or comparing two or more existing treatments.

[7] For purposes of these guidelines, a "valid analysis" is defined as an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. However, a valid analysis does not need to have a high statistical power for detecting a stated effect. The main requirements for a valid analysis are: (a) allocation of study participants of all groups to the intervention and control groups by an unbiased process such as randomization; (b) unbiased evaluation of the outcome(s) of study participants; and (c) use of unbiased statistical analysis and proper methods of inference to estimate and compare intervention effects among groups.

description of plans to conduct valid analyses of the applicable subpopulations. However, the trial is not required to provide high statistical power for these comparisons.

The NIH policy on women and minorities in clinical research requires researchers not only to design their studies to include women and minorities, but also to report to NIH how many women and minorities are planned to be enrolled, and then how many women and minorities are actually enrolled, in the study. In the initial application, the investigator must provide a targeted enrollment plan that estimates the number of subjects the researcher plans to enroll, by sex and by racial and ethnic categories. Each year thereafter, as part of the required annual progress report, the researcher must report actual enrollment of subjects by sex and racial/ethnic categories.

Implementation of the NIH policy on inclusion of women and minorities lies not only with the applicant, but also with the peer reviewers, the scientific review official, and the administering NIH institute. The applicant is responsible for designing a study to include women and minorities, describing an analysis plan that will allow for valid data on women and minorities, and reporting targeted and actual enrollment. The peer reviewers are responsible for ensuring that the applicant's plan for inclusion of women and minorities is satisfactory and follows the NIH policy. The peer reviewers must assign each scored application with one code for the inclusion of women and a second code for the inclusion of minorities.[8] For gender, each scored application will have a code that shows whether both genders, or only one, are represented in the grant, and whether the plan for gender representation is judged acceptable by the study section. For minorities, a code is also assigned to each grant by the review committee. The code shows whether minorities, non-minorities, or both were represented in the grant, and whether the plan for minority representation was judged acceptable by the study section.

The Scientific Review Officer is responsible for ensuring that the review committee assesses the inclusion of women and minorities, that the codes assigned by the study section are accurately recorded, and that the summary statement reflects the discussion of the review committee

[8] The initial scientific peer review of most research applications includes a process in which only those applications deemed by the reviewers to have the highest scientific merit, generally the top half of the applications under review, will be assigned an overall score. "Unscored" applications are not discussed or scored at the review meeting.

and accurately and completely describes any concerns expressed by the reviewers.

Should the study section assign any score containing a "U" (unacceptable) rating, the grant may not be funded until and unless the concerns of the study section are resolved. It is the responsibility of the administering institute to work with the principal investigator to modify the proposal to address any concerns and ensure compliance with the NIH policy before the grant is funded.

The NIH Policy on the Inclusion of Children in Clinical Research

As scientists, government administrators, patient advocates, and the public became more concerned about the inclusion of women and minorities in clinical research, similar concerns grew for the inclusion of children. In early 1996, the NIH noted that only 25 percent of marketed medications carried FDA-approved labeling for use in infants or children. Moreover, the statistics were even less encouraging for the drugs physicians most often used to actually treat children. Of the 80 drugs most frequently used for newborns and infants, only five (6.5 percent) were specifically labeled for pediatric use.[9] These concerns were shared by the American Academy of Pediatrics (AAP). In 1994-1995, the AAP asked the NIH to establish policies for the inclusion of children in clinical research, similar to the policies NIH was establishing related to inclusion of women and minorities. In a committee report, the U.S. House of Representatives Committee on Appropriations also encouraged the NIH to establish guidelines to include children in clinical research.[10] The clear need for rigorous clinical research evidence to support physicians' treatment decisions involving children, and the support of key advocacy groups and legislators, led the NIH to reassess the appropriate level of participation of children in clinical research.

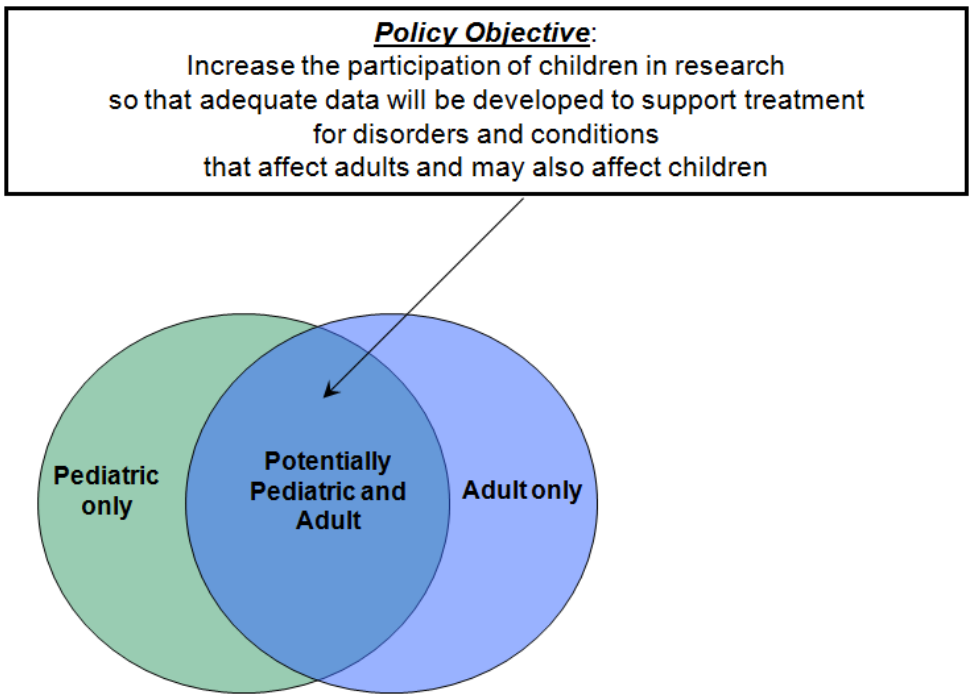
In 1996, the NICHD collaborated with the AAP to convene a workshop to review the status of the inclusion of children in NIH-sponsored clinical research. Prior to the workshop, a panel of clinical research experts reviewed a sample of new and competing FY 1994 NIH grant awards to roughly assess the extent to which "missed opportunities" may have existed for including children in NIH-funded research. The expert panel agreed that the NIH should take steps to enhance the inclusion of children in clinical research, establish a system for tracking the extent to which children are included, and provide greater education about the inclusion of children to the scientific community. To implement these

[9] U.S. Department of Health and Human Services, National Institutes of Health, Report on NIH Pediatric Research, April 1996.
[10] U.S. House of Representatives, Committee on Appropriations, House Report 104-209.

recommendations, in 1998 the NIH established a new policy on the inclusion of children in clinical research and published it in the *NIH Guide for Grants and Contracts.*[11]

The objective of the NIH policy is to increase the participation of children in research so that adequate data will be developed to support treatment for disorders and conditions that affect adults and may also affect children. As illustrated in Figure 2, the scope of the pediatric inclusion policy encompasses all research in human subjects conducted or supported by the NIH. This includes research that is considered "exempt" from the HHS policies governing the protection of human subjects. The policy's objective, however, is aimed at those conditions and processes that could potentially affect either adults or children.

Figure 2: Objectives and Scope of the NIH Pediatric Inclusion Policy



The NIH pediatric inclusion policy states that children must be included in all human subjects research, unless there are specific scientific and/or ethical reasons not to include them. The policy describes seven specific allowable reasons for the exclusion of children. If none of these reasons applies, the investigator should include children in the research. The allowable exceptions to the general rule of including children are

[11] http://grants.nih.gov/grants/guide/notice-files/not98-024.html

listed in Table 3. As is true for the policy on the inclusion of women and minorities, cost is not an acceptable reason for not including children as research subjects.

Table 3: Allowable Exceptions to the General Policy of Including Children in Research

	Allowable Reasons for Exclusion of Children
1.	The condition being studied is not relevant for children
2.	Laws or regulations exist barring inclusion of children
3.	The issue was already studied in children—including them would be redundant
4.	A separate study is warranted or preferable because of adult/child differences
5.	Insufficient data are available in adults to judge the risk to children
6.	The study is collecting additional data on pre-enrolled adult participants
7.	Other reasons that are acceptable to the review committee and IC Director

The NIH policy on the inclusion of children in research defines "children" as individuals under 21 years of age. As Table 4 shows, in the U.S. the line between childhood and adulthood is often drawn at different ages for different purposes by different organizations and agencies. The definition of childhood used by the NIH policy is consistent with that used by the AAP and the Centers for Medicare and Medicaid Services. However, it differs considerably from the definition used by the Food and Drug Administration (FDA); for purposes of drug regulation, the FDA defines adulthood at age 16 and over. For purposes of human subjects protection, the Department of Health and Human Services (HHS) defines adulthood at the legal age of consent for treatment. In most U.S. states this is 18 years, for most treatments; individuals over the age of consent in their state need not obtain parental consent to participate in research.[12]

[12] See http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102. In other documents, the age of consent is sometimes referred to as 18 years, even though this may differ in some states. In the regulations, the age of consent to research is defined as the age of consent to medical treatment.

Table 4: When Does Adulthood Begin? Differing Definitions of Adulthood for Legal, Commercial, and Regulatory Purposes

Age	Description
12-16	Age at which a minor can obtain certain specified medical services and treatment (STD, contraception, etc.) without parental consent in the U.S. (varies by state)
15-18	Age at which a minor can obtain any medical treatment without parental consent in the U.S. (varies by state)
15-18	Age at which compulsory schooling ends in the U.S. (varies by state)
15-18	Age at which family or juvenile court jurisdiction ends in the U.S. (varies by state)
16	Driving age in most U.S. states
16	Age of adulthood for FDA regulatory purposes
16-18	Age of consent in most U.S. states
16-20	Legal age of adulthood (ability to enter into legal contracts) in most developed countries
18	Legal age of adulthood in most U.S. states (a few at 17, a few at 19)
18	Age of qualification of federal benefits as an adult in the U.S.
18	Age you can join the army without parental consent in the U.S.
18	Considered adult for human subjects protection purposes in the U.S.
18	Voting age in the U.S.
18	Age of adulthood in the U.N. Convention on the Rights of a Child
21	Legal drinking age in U.S.
21	Age of adulthood for purposes of obtaining Medicare benefits
21	Age of adulthood for NIH inclusion of children policy
25	Earliest age at which many companies will rent a car to an individual with no additional driver

Under the NIH policy on the inclusion of children, specific responsibilities lie with the applicant, the peer reviewers, the scientific review officials, and the administering NIH institute. The applicant's responsibilities include designing a study that appropriately includes children (unless one of the acceptable reasons for exclusion applies), and describing the plan for including children in the application. In addition, the applicant is responsible for ensuring that the study team includes the expertise to appropriately care for child subjects. The peer reviewers are responsible for ensuring that the application meets the NIH policy, and for assigning each scored application a code with one of the values shown in Table 5. The value shows whether children, adults, or both were included in the grant, and if the plan for inclusion of children was judged acceptable by the study section.

Table 5: Codes for Inclusion of Children in Research

Code	Description
1A	Both children and adults included, scientifically acceptable
2A	Only children included, scientifically acceptable
3A	Only adults included, scientifically acceptable
4A	Inclusion of children unknown, scientifically acceptable
1U	Both children and adults included, scientifically unacceptable
2U	Only children included, scientifically unacceptable
3U	Only adults included, scientifically unacceptable
4U	Inclusion of children unknown, scientifically unacceptable
1R	Both children and adults included, scientifically resolved
2R	Only children included, scientifically resolved
3R	Only adults included, scientifically resolved
4R	Inclusion of children unknown, scientifically resolved

The scientific review administrator is responsible for ensuring that the review committee assesses the inclusion of children, that the codes assigned by the study section are accurately recorded, and that the summary statement reflects the discussion of the review committee and accurately and completely describes any concerns expressed by the reviewers.

Should the study section assign any score containing a "U" (unacceptable) rating, the grant may not be funded until and unless the concerns of the study section are resolved. It is the responsibility of the administering institute to work with the principal investigator to modify the proposal to address any concerns and ensure compliance with the NIH policy before the grant can be funded.

The NIH policy on the inclusion of children in clinical research is similar to the policies on inclusion of women and minorities in its overall purpose and its general implementation. The NIH policy on the inclusion of children, like the policies on women and minorities, requires investigators who apply for NIH support for clinical research to include children in their studies, unless there is a defensible reason otherwise. The policies are also similar in how they are implemented. Investigators are required to submit inclusion plans; review committees assess these plans for compliance with the policy, and record implementation codes; scientific review officers record the codes and the discussions of the review panels; and administering ICs must ensure any concerns arising from the review are resolved.

Despite these similarities, however, there are two crucial differences between the NIH policies on inclusion of women and minorities and the

policy on inclusion of children. First, the policy on inclusion of children – unlike the policies on women and minorities – carries with it no requirement that investigators for any study analyze differences or similarities in how groups of subjects vary in their response to an intervention. Second, the policy on inclusion of children – unlike the policies on inclusion of women and minorities – does not carry with it any requirement for reporting of actual or planned enrollment by category.

Evaluation of the NIH Policy on the Inclusion of Children

In the past decade since the establishment of the NIH policy, concerns about the inclusion of children in clinical research have continued.[13] Many commonly-used prescription drugs still lack pediatric dosing and FDA-approved pediatric labeling.[14] Similarly, data are lacking on pediatric use for medical devices. Some researchers and advocates have expressed concern that allowable exceptions to the NIH inclusion of children policy have been over-used. Others have pointed out the possibility that some researchers are nominally complying with the policy by including individuals 18-21 years, who still are counted as children under the policy, but not including younger children who may be equally appropriate subjects.[15] Data that are routinely collected through NIH administrative systems on the inclusion of children, although helpful, are insufficient to fully address these issues. Consequently, the NICHD undertook a program evaluation study to review the implementation of the NIH policy with respect to NICHD funded grants.

The NICHD is the eighth-largest of the 27 institutes and centers (ICs) that make up the NIH. Although the institute's name includes the words "child health", the NICHD does not focus exclusively on children or pediatric research. The NICHD's scientific research focuses on the normal and abnormal developmental processes throughout the life span. The mission of the NICHD is: "To ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve

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[13] For example, see Laura Bell (2008), "No Child Left Behind", Cure, 7(2), 45-51.
[14] Continued concern about the lack of pharmaceuticals specifically for use in children led the Congress to pass the Best Pharmaceuticals for Children Act (BPCA), which was signed into law on January 4, 2002. The BPCA was designed to establish a process for studying on-patent and off-patent drugs for use in pediatric populations, and to improve pediatric therapeutics through collaboration on scientific investigation, clinical study design, and ethical and labeling issues. For more information on the BPCA, see http://bpca.nichd.nih.gov/index.cfm.
[15] For example, see Daniel P. Gitterman et al, 2004. "Did a Rising Tide Lift All Boats? The NIH Budget and Pediatric Research Portfolio", Health Affairs, 23(5), 113-124.

their full potential for healthy and productive lives, free from disease or disability, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation"[16]. This broad mission means that many of the NICHD's research activities fall in the area of most interest for the NIH policy – that is, conditions and issues that may affect both adults and children.

The key questions to be addressed by this evaluation study were:

1. When conducting human subjects research on conditions that affect both adults and children ("relevant conditions"), how frequently did NICHD applicants and grantees propose to include children in their clinical studies, and what age groups were included?

2. In what percentage of the relevant NICHD grants and applications that included children did the PI indicate an intention to analyze outcome data by age or age groups?

3. In what percentage of the relevant NICHD grants and applications did researchers propose to include only certain groups of children (i.e. only children over 18 but under 21, or only children where parental consent would not be required)?

4. When researchers proposed to include only adults, what were the reasons given for the exclusion of children?

5. How did study sections implement the NIH policy on the inclusion of children for relevant NICHD grants?

To answer these questions, we reviewed a total of 397 NICHD-funded type 1 and type 2 (new and recompeting) grant proposals with human subjects.[17] A separate review was conducted including NICHD 2007 type 1 and 2 grant applications that were deemed "unacceptable" by the study section for the inclusion of children, whether the application was funded or not. These reviews were designed to analyze application data that would address questions about how study sections implemented the NIH policy.

The reviews were conducted by a multidisciplinary team that included staff from the NICHD Office of Science Policy, Analysis and

[16] http://www.nichd.nih.gov/about/overview/mission/index.cfm
[17] A small number of applications related to conditions where only children could be affected were excluded.

Communications, and two contractors, MasiMax Resources Ltd. and The Madrillon Group, Inc.[18] Each grant application was reviewed in its entirety, and where applicable, summary statements were reviewed as well. The team developed a detailed protocol and created a SQL database to collect and record information about the ages of subjects included, the investigator's plan to analyze data by age, and the reasons given for inclusion or exclusion of child subjects. Additional data on each grant -- including research mechanism, program class code, PI degree, priority score, and study section – were downloaded from NIH administrative systems to augment the data obtained from the grant review.

The project included an initial pilot phase to develop and refine the protocol for data collection, followed by three additional data collection waves. During the pilot phase, each application was reviewed in its entirety and data were recorded independently by all seven team members. Discrepancies were then identified, discussed, and reconciled. During this pilot phase, standardized rules were developed and refined to cover those situations where the applicant used less precise terms to describe the ages of subjects, such as "middle school children". Examples of some of the most frequently used standardized rules are given in Figure 6. Twenty applications were included in the pilot phase of the study.

Figure 6: Examples of Standardized Rules Used to Classify Ages of Research Subjects

- "infants" were classified as children age 0 to 1 year.
- "toddlers" were classified as children age 1 to 4 years.
- "elementary school" children were classified as children age 5 to 13 years.
- "high school children" were classified as children age 14 to 18 years.
- "school age children" were classified as children age 5 to 18 years.
- "pre-teens", "prepubescent", and "tweens" were classified as children age 8 to 12 years.
- "adolescents" or "teens" were classified as children age 13 to 19 years.
- "college students" were classified as age 17 years or older.
- "parents", "mothers", or "fathers" – if not explicitly excluding individuals under 21 were assigned an age range that began at 15 years + the age of the oldest child. For example, parents of infants could be 15 years or older, where parents of 5 year olds would be 20 years or older.
- "reproductive age" – if not explicitly excluding individuals under 21 – was classified as 15 years or older.

[18] The team included individuals with medical, legal, social science, and public health backgrounds.

Once the protocol had been pilot tested by the entire team, the study was implemented in three waves of data collection to ensure quality control. Each wave included between 119 and 129 grants. Grants were stratified by research mechanism and application type (new or recompeting). Grants within each stratum were randomly assigned to each wave. Rigorous and detailed procedures for quality control were employed for all three waves. A single lead coder was assigned to all grants. Based on the research mechanism, wave, and application type, each grant was assigned a probability of selection for additional review by a second and third coder. Subsequently, grants were randomly selected for additional review. Applications for multi-project or center grants, which tended to have longer and more complex applications, were more likely to be selected for additional review. The probability of additional reviews were set higher for the first wave, and then decreased in subsequent waves. Table 7 shows the numbers and percentages of grants selected for review by one, two, or three coders by wave. Including the pilot phase grants, 34 percent of the grants in the overall sample were reviewed by multiple coders. Each coder was blinded to the data recorded by the others. Moreover, any application for which the coders felt that there was an ambiguity or question was brought to the full team for discussion at the end of each wave. At the conclusion of this review process, a total of 397 grant applications had been reviewed with an inter-rater reliability of 94 percent.

Table 7: Number and Percent of Grants by Number of Coders, by Wave

	Pilot	Wave 1			Wave 2			Wave 3		
Number of Coders	7	1	2	3	1	2	3	1	2	3
Number of Grants	20	77	33	19	90	26	13	99	15	5
Percent of Grants in Wave	100	60	26	14	70	20	10	83	12	5

Note: percentages may not add to 100 because of rounding.

The team reviewed the NIH administrative data to identify grants rated "unacceptable" by the study sections. For each of these grants that were assigned to the NICHD, the summary statement was reviewed and the reasons for the unacceptable rating were recorded. The NIH administrative data on inclusion of children were also analyzed, to determine rates of inclusion of children for each individual NIH institute or center.

Descriptive statistics were calculated to answer each of the evaluation questions. Associations between characteristics of the grant (research mechanism and subject matter), characteristics of the principal investigator (degree), and the inclusion of children were assessed with bivariate and multivariate analyses. The results were reported as bivariate analyses only because small cell sizes and multicollinearity among the study variables made interpretation of the multivariate analyses difficult.

A key limitation of the study was that the information available to the team included only what was available in the application and summary statement of the grant. Consequently, the assessment was limited to the investigators' intent and plan to include children – not whether the investigators actually did include children in their research. Moreover, the results of the analysis were limited to the NICHD and not necessarily generalizable to the rest of the NIH. However, as described below, the limited data that were available from NIH systems on inclusion of children at other institutes were also reviewed.[19]

Inclusion of Children in NICHD Research

Institutes and centers across the NIH varied in the percent of their grants that involved human subjects and the percent of these grants where children under 21 years of age were included. These data are shown in Table 8. Institutes such as the National Institute on Drug Abuse (NIDA), the NICHD, the National Center for Research Resources (NCRR), and the National Institute of Mental Health (NIMH) funded the highest proportion of grants that included children, while the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) were less likely to fund grants that included children.

[19] In addition, a small sample of grants from NCI were also reviewed and coded to pilot test the methodology for other NIH ICs. The pilot test showed that the methodology could be applicable NIH-wide.

Table 8: Inclusion of Children Under 21 by NIH Institute or Center

Institute or Center	Number of Eligible Grants*	Percent of Eligible Grants Including Children under 21
NIDA	349	87
NCRR	107	87
NIMH	626	84
NICHD	397	83
NIDCD	147	77
NIAAA	141	76
NIAID	417	74
NCMHD	46	74
NEI	93	72
FIC	37	68
NINDS	251	65
NINR	160	62
NIDDK	326	61
NHLBI	493	57
NIAMS	124	57
NIDCR	100	56
NIGMS	101	54
NIEHS	95	53
NIBIB	92	51
NCI	758	47
NHGRI	34	47
NCCAM	59	43
NLM	42	23
NIA	312	18

*Eligible grants are human subjects type 1 and 2 funded grants in FY 2007.
Source: NIH Administrative data

For NICHD grants, inclusion was assessed for children under age 21 and for children under age 18. Table 9 shows the inclusion of children for NICHD funded grants.[20] Although 87 percent of NICHD human subjects grants included children under 21, nearly 22 percent included only subjects 18-20 and not subjects under 18. About 13 percent of NICHD human subjects grants excluded children altogether, with no subjects under 21 years old.

[20] The numbers in Tables 8 and 9 for NICHD differ because of coding errors in the NIH administrative data. In our review we discovered that 6.3 percent of NICHD grants were coded incorrectly. Most often, these errors occurred when a grant was coded as not including children under 21, yet children 18-20 years of age were included.

Table 9: Inclusion of Children for NICHD Funded Grants, FY 2007

Age Group Included	Number of Grants	Percent of All Grants	
Under 18	259	65.2	87.1 percent include children under 21
18 and over only	87	21.9	
21 and over only	51	12.9	12.9 percent exclude children under 21
Total	397	100.0	

Several characteristics were associated with whether a research project is likely to include children under 18 or under 21. One major factor was the research mechanism, as shown in Table 10. R01 grants were most likely to include children, followed by center grants and co-operative agreement (P and U) mechanisms. Individual training and career development (F and K) grants, and smaller research grants (R03 and R21), which typically involve smaller funding amounts compared with R01s, were less likely to include children. Small business (SBIR/STTR) grants were least likely to include children.

Table 10: Inclusion of Children by Research Mechanism

	F + K		P + U		SBIR/STTR (R41-R44)	
	Number of Grants	Percent of Grants	Number of Grants	Percent of Grants	Number of Grants	Percent of Grants
Grants that include children under 18	28	58.4	29	70.7	25	54.3
Grants that include only "children" 18 and over	10	20.8	12	29.3	7	15.2
Grants that include only 21 and over	10	20.8	0	0.0	14	31.5
Totals	48	100.0	41	100.0	46	100.0

	R01		R03/ R21		Other R	
	Number of Grants	Percent of Grants	Number of Grants	Percent of Grants	Number of Grants	Percent of Grants
Grants that include children under 18	110	75.9	63	60.0	4	33.3
Grants that include only "children" 18 and over	31	21.4	23	21.9	6	50.0
Grants that include only 21 and over	4	2.7	19	18.1	2	17.7
Totals	145	100.0	105	100.0	12	100.0

As might be expected, the inclusion of children was also associated with the subject matter of the grant. This was reflected in the differences in the inclusion of children across organizational units of the NICHD. For example, as shown in Table 11, grants assigned to the NICHD's Child Development and Behavior Branch, located in the Center for Mothers and Children, were more likely to include children than grants assigned to other branches. (The Child Development and Behavior branch supports research on child development, school readiness, learning disabilities, and other topics related to children's intellectual growth and development.) By contrast, grants that were assigned to branches within the National Center of Medical Rehabilitation Research (NCMRR) were less likely to include children. The NCMRR supports research on rehabilitation following injury or illness, such as traumatic brain injury, stroke, or other conditions. Although many of these conditions do affect children, the emphasis on pediatric research is less pronounced.

Table 11: Inclusion of Children by Selected NICHD Organizational Units

Center for Research on Mothers and Children	Child Development and Behavior (CDB)		Endocrinology, Nutrition and Growth (ENG)	
	Number of Grants	Percent of CDB Grants	Number of Grants	Percent of ENG Grants
Grants that include children under 18	71	83.5	31	96.9
Grants that include only "children" 18 and over	9	10.6	1	3.1
Grants that include only 21 and over	5	5.9	0	0.0
Totals	85	100.0	32	100.0
Center for Population Research	**Demographic and Behavioral Sciences (DBS)**		**Reproductive Sciences (RS)**	
	Number of Grants	Percent of DBS Grants	Number of Grants	Percent of RS Grants
Grants that include children under 18	40	58.0	9	31.0
Grants that include only "children" 18 and over	21	30.4	15	51.7
Grants that include only 21 and over	8	11.6	5	17.3
Totals	69	100.0	29	100.0
Center for Developmental Biology and Perinatal Medicine	**Intellectual and Developmental Disabilities (IDD)**		**Pregnancy and Perinatology (PP)**	
	Number of Grants	Percent of IDD Grants	Number of Grants	Percent of PP Grants
Grants that include children under 18	34	87.2	13	72.2
Grants that include only "children" 18 and over	4	10.3	4	22.2
Grants that include only 21 and over	1	2.5	1	5.6
Totals	39	100.0	18	100.0

National Center for Medical Rehabilitation Research		
	Number of Grants	Percent of NCMRR Grants
Grants that include children under 18	29	34.9
Grants that include only "children" 18 and over	25	30.1
Grants that include only 21 and over	29	35.0
Totals	83	100.0

Note: not all NICHD organizational units were included in this chart. Those units that had a small number (less than 15) of new and recompeting funded clinical research grants in FY 2007 were excluded.

The differences in the inclusion of children across organizational units, and across research mechanisms, each appear to independently contribute to the variation in the inclusion of children. Although the individual cell sizes were too small to draw firm conclusions, the pattern of differences between R01 and SBIR/STTR mechanisms appeared to persist across organizational units. Moreover, differences across organizational units also persisted within the R01, center, and training mechanisms.

PI degree was also associated with inclusion of children. Table 12 shows the inclusion of children by PI degree. Investigators with an MD degree were more likely to include children than investigators with a PhD degree only.

Table 12: Inclusion of Children by PI Degree

	MD only		PhD only		MD + PhD		Other *	
	Number of Grants	Percent of Grants	Number of Grants	Percent of Grants	Number of Grants	Percent of Grants	Number of Grants	Percent of Grants
Grants that include children under 18	59	74.7	158	63.2	18	75.0	19	54.3
Grants that include only "children" 18 and over	17	21.5	57	22.8	5	20.8	7	20.0
Grants that include only 21 and over	3	3.8	35	14.0	1	4.2	9	25.7
Totals	79	100.0	250	100.0	24	100.0	35	100.0

Note: "Other" includes such doctoral level degrees as DDS/DMD (dental), DVM (veterinary), JD (law), individuals without graduate degrees, and others. For 7 grants, PI degree information was not available, and these grants are not included in any of the above categories.

A weak association was also found between priority score and the inclusion of children, with grants that included children receiving slightly more favorable mean and median priority scores. However, the differences were small.

Most individual study sections reviewed only two to four funded NICHD new and recompeting grants in FY 2007. As a result, it was not possible to draw general conclusions about the inclusion of children across study sections. The few differences that could be observed were entirely consistent with subject matter differences. For example, the NICHD-run Child Health and Human Development group, which includes many topics relevant to pediatrics, reviewed grants that were more likely to include children when compared with the CSR's Musculoskeletal Rehabilitation Sciences study section, a standing review group that reviewed grants related to rehabilitation.

Analysis of Data by Age in NICHD Research that Includes Children

Ultimately, the goal of the NIH policy on the inclusion of children is to strengthen the evidence base that clinicians rely on for the prevention, diagnosis, and treatment of disease in children. To accomplish this goal, it would not be sufficient to simply include children in the research projects – it would also be necessary to analyze research data related to the ages of the subjects, to help identify how appropriate interventions may differ between children and adults. Studies that incorporated only a few children and then pooled all subject data together for analysis, regardless of age differences, would not produce the data needed to determine if prevention or treatment interventions could work specifically in children.

For those NICHD grants that included children under 21, we reviewed the entire grant proposal to identify if the researchers proposed to analyze the data by the age of the subjects. As shown in Table 13, about half of the grants that included individuals under 21 incorporated a specific hypothesis related to age, or included age as a covariate in one or more analyses. In another one-third of cases, the investigator made no mention of any plan to analyze data by age. A smaller number of proposals mentioned the possibility of analyzing data by age, but did not state a definite plan to do so. Finally, in 7.5 percent of the applications, the study was constructed with a narrow age range of subjects – 3 or fewer years – making analysis by age less useful or practical for understanding differences by developmental stage.

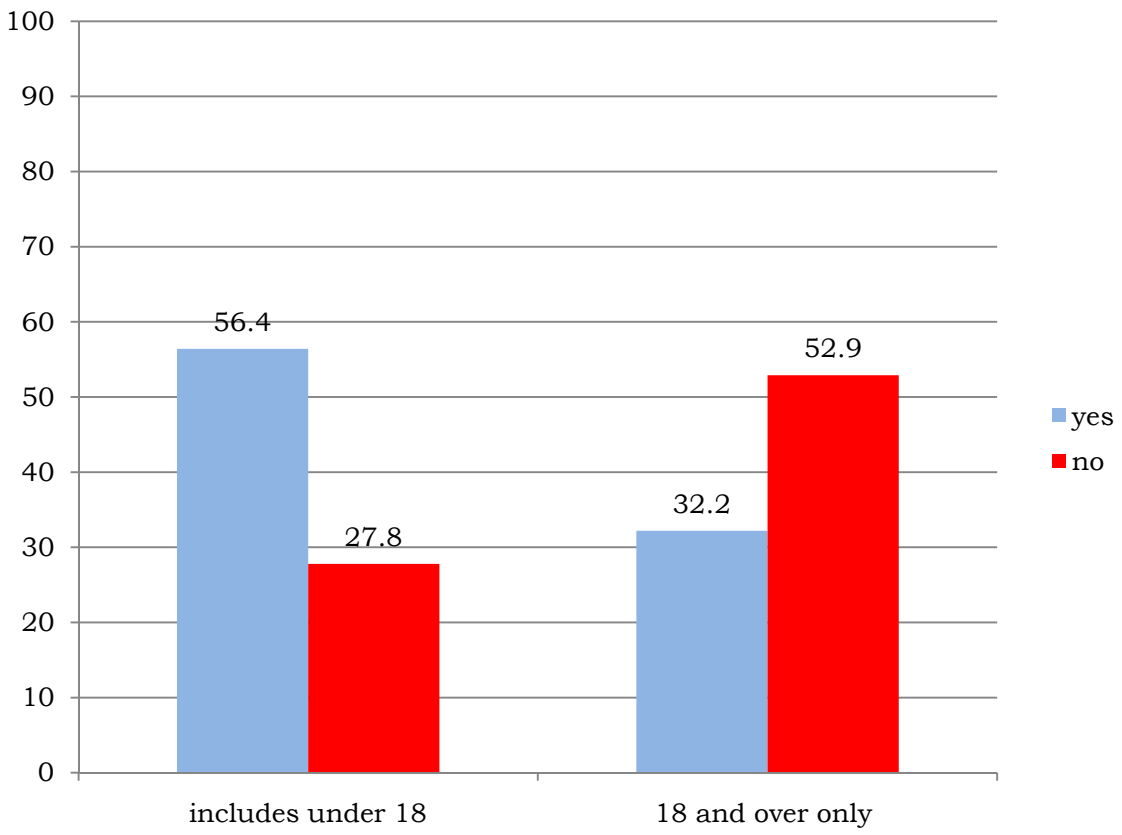
Table 13: Plans for Analysis by Age, for NICHD Grants Including Children Under 21, FY 2007

Analyze by age?	Description	Number of grants	Percent of grants
Yes	Application includes a specific hypothesis that involves analyzing age, or age is specified as a control variable in the analysis plan	174	50.3
No	There is no mention in the application of any plan to analyze any data by age or age group.	118	34.1
Maybe	The application states that the data may or may not be analyzed by age	28	8.1
Not applicable	The data are being collected on a sample that is restricted to an age span of 3 years or less	26	7.5
	Totals	346	100.0

When an analysis plan was in place, the PI generally proposed to analyze data by all the child subjects' ages, rather than conducting age-related analyses for only a subset of research subjects. In 92 percent of these applications that included children and proposed analysis by age, the age analysis included the full age ranges of subjects in the study.

Grants that included only children 18 years and over were less likely to analyze data by the age of research subjects, compared with grants that included children under 18. As shown in Figure 14, more than half of grants that included children under 18 proposed to analyze their data by age, while only one third of grants that include only individuals 18 and over proposed to analyze the data by age.

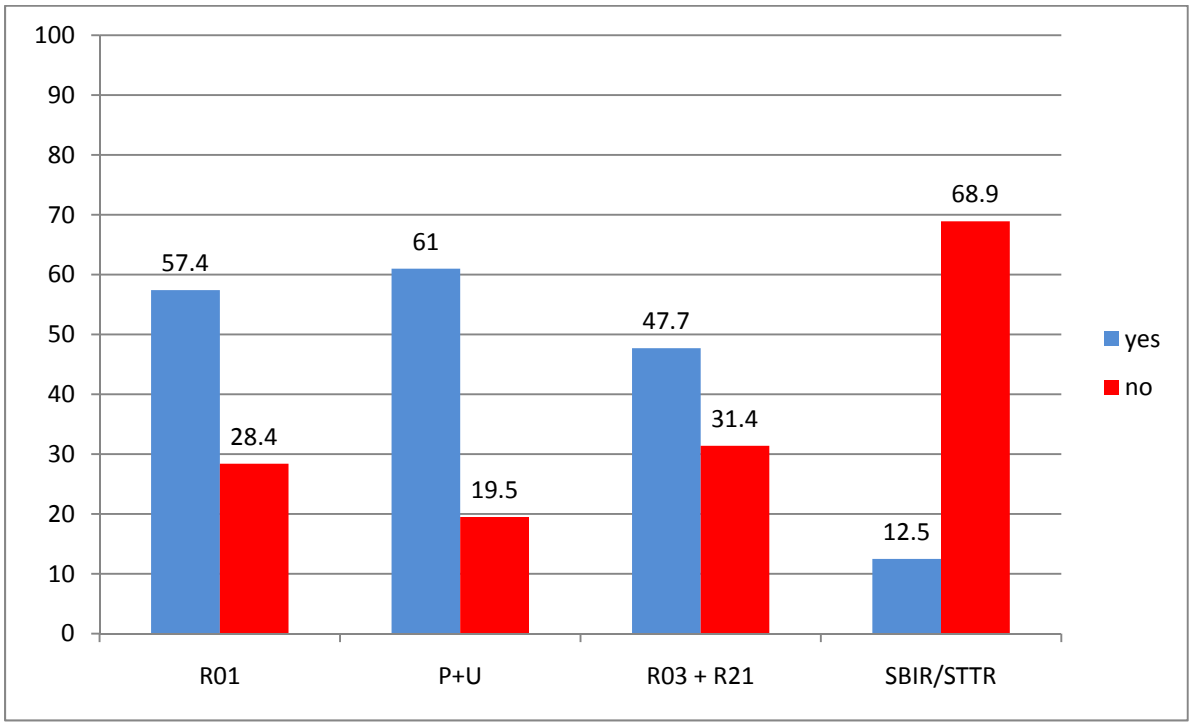
Figure 14: Plans for Analysis by Age, for NICHD Grants Including or Excluding Children Under 18, FY 2007



Note: "yes" and "no" categories do not add up to 100 percent; "maybe" and "not applicable" categories are not shown.

As was the case with the inclusion of children, several characteristics were associated with plans to analyze data by children's age, and the most important of these were research mechanism and subject matter. As shown in Figure 15, the larger NIH grants – R01s, centers (P) and cooperative agreements (U) – were most likely to include a plan to analyze data by age. Small business grants, however, were significantly less likely to include a plan to analyze data by age.

Figure 15: Age Analysis Plan by Research Mechanism, for NICHD Grants that Included Children Under 21, FY 2007



Note: "yes" and "no" categories do not add up to 100 percent; "maybe" and "not applicable" categories are not shown.

Subject matter also seemed to play a substantive role in whether an investigator planned to analyze data by age. Table 16 shows the distribution of age analysis plans by NICHD center and/or branch. As was the case of inclusion of children, grants on topics mainly concerned with children, such as Child Development and Behavior, were more likely to analyze data by age compared with other areas, such as rehabilitation research.

Table 16: Age Analysis Plan by NICHD Center or Branch, for Grants that Included Children Under 21, FY 2007

Center for Research on Mothers and Children	Child Development and Behavior (CDB)		Endocrinology, Nutrition and Growth (ENG)	
	Number of Grants	Percent of CDB Grants	Number of Grants	Percent of ENG Grants
Yes	59	69.5	12	46.2
No	13	15.3	6	23.1
Maybe	1	1.1	3	11.5
Not Applicable	12	14.1	5	19.2
Totals	85	100.0	26	100.0

Center for Population Research	Demographic and Behavioral Sciences (DBS)		Reproductive Sciences (RS)	
	Number of Grants	Percent of DBS Grants	Number of Grants	Percent of RS Grants
Yes	40	57.2	9	37.5
No	21	30.0	10	41.7
Maybe	8	11.4	5	20.8
Not Applicable	1	1.4	0	0.0
Totals	70	100.0	24	100.0

Center for Developmental Biology and Perinatal Medicine	Intellectual and Developmental Disabilities (IDD)		Pregnancy and Perinatology (PP)	
	Number of Grants	Percent of IDD Grants	Number of Grants	Percent of PP Grants
Yes	19	42.2	8	47.1
No	14	31.2	7	41.1
Maybe	2	4.4	1	5.9
Not Applicable	10	22.2	1	5.9
Totals	45	100.0	17	100.0

National Center for Medical Rehabilitation Research		
	Number of Grants	Percent of NCMRR Grants
Yes	17	31.5
No	33	61.1
Maybe	3	5.6
Not Applicable	1	1.8
Totals	54	100.0

Note: not all NICHD organizational units were included in this chart because those units that had a small number (less than 15) of new and recompeting funded clinical research grants in FY 2007 were excluded.

Unlike the inclusion of children, the analysis of data by age was not associated with PI degree. PIs with an MD and PIs with a PhD were equally likely (53 and 54 percent) to propose an analysis plan that included the age of the subjects. In addition, the mean and median priority scores with and without an analysis plan that included age were very close.

Exclusion of Children in NICHD Research Grants

The NIH policy on the inclusion of children provides for seven distinct allowable reasons for the exclusion of children as research subjects. These reasons (shown earlier in Table 3) were designed to take into account the special circumstances researchers may find when considering the inclusion of children in research studies. For example, the policy states that if the condition being studied is not relevant for children, then it is acceptable to exclude them. Legal and ethical reasons were also mentioned – for example, if insufficient data were available to judge the risk the study may pose in children, exclusion of children would be warranted. However, cost is not one of the allowable reasons for the exclusion of children from research studies.

For each of the NICHD funded grants that excluded children under 21, we reviewed the grant application in its entirety to identify the reasons given for not including children in the study. As shown in Table 17, only two reasons were used frequently. First, in over half the cases PIs stated that the condition being studied was not relevant for children. Second, over one-third of PIs concluded that a separate study would be warranted or preferable because of differences between children and adults.[21]

[21] In Taylor (2009), IRB administrators were asked whether they had reviewed studies that excluded children, and if so what were the reasons given for exclusion. The two reasons found in this study were identified by the majority of respondents. However, other reasons were also cited. These others included laws and regulations barring inclusion of children, and one reason not among the acceptable ones provided by the NIH for the exclusion of children – that "the scientific question requires the same or a comparable study population as that used in an earlier study and the potential gain in scientific knowledge outweighs the imbalance in the study population." See Holly A. Taylor (2009). "Inclusion of Women, Minorities and Children in Clinical Trials: Opinions of Research Ethics Board Administrators", Journal of Empirical Research on Human Research Ethics, 65-73.

Table 17: Reasons Cited for Exclusion of Children Under 21 from NICHD Funded Studies, FY 2007

Reason	Number of grants	Percent of grants
1. The condition being studied is not relevant for children	26	51.0
2. Laws or regulations exist barring inclusion of children	0	0.0
3. The issue was already studied in children – including them would be redundant	0	0.0
4. A separate study is warranted or preferable because of adult/child differences	18	35.3
5. Insufficient data are available in adults to judge the risk to children	1	1.9
6. The study is collecting additional data on pre-enrolled adult participants	1	1.9
7. Other reasons that are acceptable to the review committee and the IC Director	5	9.8
Totals	51	100.0

Figure 18 provides specific examples of the justifications given by investigators for the exclusion of children under 21 related to reason 1– the condition is not relevant to children.

Figure 18: Justifications Provided by Investigators for Reason #1 for Use of Adults Only, NICHD Grants, FY 2007

Children were not included in the population of interest for the study – the condition is not relevant for children
• "Strokes are primarily a problem for aged people" • The study did not include children because the program being tested would only apply to health care professionals over the age of 21. • Children were excluded from the study because "only 1-2% of women experience menopause before the age of 40." • Children were excluded because the study is focused on prospective adoptive/foster parents. • The study was focused on parents of children who are at least 8 years old and the parents, not the children, are the subjects. • Children were excluded because of "the relatively small number of children who have lower limb amputations" and because the large size of the device would not be appropriate for use in children. • "There is considerable uncertainty as to the prevalence of diabetic neuropathy in the pediatric age group. This could be because pediatric patients with diabetes show fewer symptoms of neurological involvement. Based on this information, the feasibility of the study, and the short project time, children will be excluded." • Children were excluded because "Parkinson's is primarily a problem for aged persons" • Children were excluded because "individuals with ALS are seldom less than 21 years old."

Figure 19 shows specific examples of the justifications provided by investigators for the exclusion of children under 21 related to reason 4 – a separate study is warranted or preferable.

Figure 19: Justifications Provided by Investigators for Reason #4 for Use of Adults Only, NICHD Grants, FY 2007

Children presented confounding factors (i.e. a separate study was warranted or preferable)
• "Differences have been noted between walking characteristics of children and adults"; thus a separate study would be needed to study the proposed device in children. • "Development of coordination for 'reaching movements' continues non-linearly through at least 15 years old; because such non-uniform age dependent differences in performance could confound the interpretation of data, subjects between 22 and 70 will be included." • Children were excluded because they are not "skeletally mature" • Children under 21 were excluded because "children's motor electrophysiology differs from adults" • "Children under 21 were excluded because cognitive skills, neural recognition potential, and etiologies of stroke are likely to be different for children and adolescents versus adults" • "Restricted sample to men and women age 21 and older is also necessary to accurately describe adult intentional childbearing experiences which may differ from youth because of the stigma associated with youth pregnancies, and psychological differences in adult versus youth decision making processes."

Under the NIH policy, investigators are required to provide a justification for excluding children under 21 from research studies. However, researchers who include only subjects 18 and over are including children under the NIH policy, because they are including children under 21. Nonetheless, we reviewed applications that included subjects age 18-21, but excluded children under 18, to identify their reasons for excluding children under 18. Of these studies, slightly less than half – 45 percent – provided a justification for excluding children under 18. As shown in Table 20, these justifications were generally similar to the explanations given by investigators for the exclusion of children under 21.

Table 20: Reasons Cited for Exclusion of Children Under 18 from NICHD Funded Studies, FY 2007

Reason	Number of grants	Percent of grants
1. The condition being studied is not relevant for children	18	20.7
2. Laws or regulations exist barring inclusion of children	0	0.0
3. The issue was already studied in children – including them would be redundant	0	0.0
4. A separate study is warranted or preferable because of adult/child differences	14	16.1
5. Insufficient data are available in adults to judge the risk to children	1	1.1
6. The study is collecting additional data on pre-enrolled adult participants	0	0.0
7. Other reasons that are acceptable to the review committee and IC Director	6	5.7
No reason given	48	55.2
Totals	87	100.0

Figure 21 provides specific examples of the justifications given by investigators for excluding children under 18 related to reason 1 - the condition is not relevant to children.

Figure 21: Justifications Provided by Investigators for Reason #1 for Use of Subjects Over 18 Years Only, NICHD Grants, FY 2007

Children were not included in population of interest for the study – the condition is not relevant for children
• Children under 18 were not included since "pressure ulcer formation is not an issue in this age group" • Children under 18 were excluded because the "study is targeting the adult bilingual education system" • "In vitro fertilization is generally not applicable to children under 18" • Children under 18 were excluded "because children represent a small proportion of the clients at the participating clinics, and issues are distinctly different for adults compared to children and adolescents" • Children under 18 were excluded because "it is inappropriate to provide infertility treatments to them" • " the topic concerns the acquisition of a 2nd language by adults who learned a 1st language as children".

Figure 22 shows specific examples of the justifications given by investigators for excluding children under 18 related to reason 4 - a separate study is warranted or preferable.

Figure 22: Justifications Provided by Investigators for Reason #4 for Use of Subjects Over 18 Years Only, NICHD Grants, FY 2007

Children presented confounding factors (i.e. a separate study was warranted or preferable)
• "Ultrasound and biopsy process would be inappropriately invasive for younger females" • "The study is focused on individuals who have reached full neurological development." • "Below 18 years of age, musculoskeletal development is still occurring."

Figure 23 provides an example of the justification provided by investigators for excluding children under 18 related to reason 5 – insufficient data to judge risk in children.

Figure 23: Justification Provided by Investigators for Reason #5 for Use of Subjects Over 18 Years Only, NICHD Grants, FY 2007

Insufficient information available to judge risk for children
• "[The company] has not yet produced valves in small sizes for young children, and believes that initial tests should be performed in subjects having sufficient maturity to understand the hazards of the device"

Figure 24 provides examples of the justifications given by investigators for excluding children under 18 related to reason 7 – other reasons are acceptable. Justifications provided under reason 7 were often related to convenience and/or availability of resources.

Figure 24: Justifications Provided by Investigators for Reason #7 for Use of Subjects Over 18 Years Only, NICHD Grants, FY 2007

Convenience and/or Resources
• Kids under 18 were to be excluded because "obtaining written permission from parents would be difficult…retention of older children under 18 is more difficult…"
• Including those under 18 "would require significant amounts of additional time and resources…"
• "There are also issues regarding proof of emancipated minor status and parental consent."
• "Due to topic sensitivity in the proposed research and mandatory reporting laws for reporting physical or sexual abuse among children under the age of 18 years, females in this age group will not be included."

Grants Rated "Unacceptable" on the Inclusion of Children

Across NIH institutes, between 1 and 3 percent of scored grant applications were rated "unacceptable" by the study section for the inclusion of children. At the NICHD, 1 percent of scored applications – a total of 24 – were rated unacceptable in FY 2007.[22] Three of these

[22] In a survey of study section members, Taylor (2008) found that 72 percent of study section members reported that the grants they reviewed were compliant with the NIH

applications received scores in a fundable range. For those 3 applications, the concerns were addressed and the applications were ultimately funded.

For each of the NICHD applications deemed "unacceptable", the summary statement was reviewed to identify the reasons for the unacceptable rating. The reasons given are shown in Table 25, and additional detail is provided in Table 26. The most common reason for an unacceptable rating is that no justification was provided for the exclusion of children. Interestingly, in a number of instances the study section made this comment in cases where subjects between 18 and 21 were included. In some other cases, the researchers did not provide information in their application about the ages of the proposed research subjects.

Although only a few grants were rated unacceptable, several variables appeared to be associated with receiving a rating of unacceptable. For example, PIs with PhD degrees were over-represented in the group of PIs with grants rated "unacceptable" ratings – 19 of these 24 grants (79 percent) had PIs with a PhD degree. Similarly, small business SBIR/STTR grants were more likely to have an unacceptable rating – 6 of these 24 grants (25 percent) were SBIR/STTR grants, although these grants account for only 2.5 percent of NIH funding. Finally, one study section accounted for 5 of the 24 unacceptable grants, or 20.8 percent.

Table 25: Categories of Reasons Given for "Unacceptable" Ratings from NIH Study Sections

Categories	Number of grants	Percent of grants
No justification was provided for the exclusion of children	11	46
The ages of the subjects were not given	8	33
Concerns about the adequacy of human subjects protections	2	8
Other	3	13
Totals	24	100.0

policy on the inclusion of children. However, less than half (48 percent) reported frequently discussing the inclusion of children at study section meetings. See Holly A. Taylor (2008). "Implementation of NIH Inclusion Guidelines: Survey of NIH Study Section Members", Clinical Trials, 5, 140-146.

Table 26 shows specific examples of the reasons provided by study sections for rating grants "unacceptable" for inclusion of children, grouped by the categories above.

Table 26: Study Section Descriptions for Grants Rated "Unacceptable" for Inclusion of Children

	Grant Mech.	Children Code	Reason for Unacceptable (Direct Quotes from Summary Statements)	Category
1.	F32	4U	Ages of the subjects are not described.	ages not given or not clear
2.	K01	4U	Study participants will be as young as 18 years of age yet the PIs state that children will not be included.	ages not given or not clear
3.	R01	4U	Information on ages of subjects is not provided.	ages not given or not clear
4.	R01	4U	The ages of the mothers donating milk is not addressed in the application. It is unclear if children (individuals under 21-years-old) will be included or whether this information will be known to the PI.	ages not given or not clear
5.	R01	4U	No information about subject ages is presented.	ages not given or not clear
6.	R03	4U	The inclusion of children (females 18 years old and older) is unknown.	ages not given or not clear
7.	R21	4U	Ages of subjects are not presented.	ages not given or not clear
8.	R21	4U	More information is needed.	ages not given or not clear
9.	R01	4U	There is no section on the protection of human subjects from research risks.	human subjects protection
10.	R43	1R	Information needed about investigator's use of informed consent procedures for children under 18.	human subjects protection

	Grant Mech.	Children Code	Reason for Unacceptable (Direct Quotes from Summary Statements)	Category
11.	F32	3U	The exclusion of children is not sufficiently justified, particularly given the fact that children between the ages of 18 and 21 can and have successfully participated in studies similar to those proposed.	no justification for exclusion
12.	K23	1U	The exclusion of persons with TBI younger than 18 is not justified.	no justification for exclusion
13.	P01	1U	Justification for the ages of study subjects is provided. However, for project 1/study 2 the reasons for excluding children younger than 18 years of age are not clearly articulated.	no justification for exclusion
14.	R03	1U	This study will include individuals 18 years and older. No rationale for the age range is given.	no justification for exclusion
15.	R03	3U	A scientific rationale for the exclusion of children should be given.	no justification for exclusion
16.	R03	3U	The rationale for the selected age range needs to be stated.	no justification for exclusion
17.	R21	3U	No children will be studied and all participants will be at least 21 years old.	no justification for exclusion
18.	R43	3U	The exclusion of children is not sufficiently justified.	no justification for exclusion
19.	R43	4U	Lack of inclusion of children is not adequately justified.	no justification for exclusion
20.	R43	3U	Lack of inclusion of children is not justified.	no justification for exclusion
21.	R43	1R	Inadequate justification for exclusion of children.	no justification for exclusion

	Grant Mech.	Children Code	Reason for Unacceptable (Direct Quotes from Summary Statements)	Category
22.	F32	1U	All of the participants will be children between three and four years old. The use of children is appropriate and scientifically justifiable, but the application uses an IRB application in place of the required specific inclusion plan, and this is inappropriate.	other
23.	R43	1R	No inclusion of children plan was provided.	other
24.	U54	4U	No specific reason was given for the unacceptable rating.	other

Summary and Conclusions

Although the institute's name includes the words "child health", the NICHD does not focus exclusively on children or pediatric research. The NICHD's scientific research focuses on the normal and abnormal developmental processes throughout the life span. The NIH pediatric inclusion policy is most relevant for conditions and issues that may affect both adults and children. Because of NICHD's broad mission, most of the Institute's activities fall in this category. The NICHD conducted a study of how the NIH pediatric inclusion policy was implemented for grants that were funded by the NICHD in FY 2007 and could include adults, children, or both.

The review showed that children were included in NICHD grants:

- 87 percent of NICHD grants included individuals under age 21, while 13 percent included only individuals over age 21;
- 65 percent of NICHD grants included individuals under age 18, while 35 percent included individuals only over 18.

When children are excluded from research, the most common reasons given were that the research was not applicable to children or that a separate study may be preferable.

Researchers and child advocates have raised concerns that investigators may be complying with the letter of the NIH policy, but not its spirit, by including "children" age 18-21 but not children under 18. This strategy may be desirable for investigators because individuals 18 years and over

do not require an additional parental consent process to participate in clinical research.[23] If the only children included in the research grants are those age 18 and over, the research results would not necessarily be generalizable to children under 18. The results of this review showed some evidence for this concern, because a full 22 percent of the NICHD grants complied with the NIH policy, but only by including children 18 or older. Over half of these "18 +" grants provided no reason for restricting eligible research subjects to those age 18 and over. However, of those that did provide a justification, only a few (6 percent) directly cited reasons of convenience or cost for choosing only subjects over 18 years of age.

It became clear during the review that neither applicants nor reviewers consistently defined adulthood at age 21 and over. In a number of applications and summary statements, researchers and/or reviewers made comments like "the inclusion of children is not applicable to this study because all subjects will be age 18 and over". This suggests that further education on the policy may be beneficial for both applicants and reviewers.

Although a large number of researchers did include children in their research, many did not plan to analyze their data in a way that would shed light on differences or similarities between children and adults. Further discussion and education in the scientific community may be appropriate about the prevalence and importance of certain conditions among children and the benefits of including them in broader research.

The review found that certain variables – most notably research mechanism and subject matter – were associated with including or excluding children, and with receiving an "unacceptable" rating by the study section for the inclusion of children. For example, SBIR/STTR applicants were: 1) less likely to include children; 2) were less likely to analyze data by age; and 3) were more likely to receive an unacceptable rating. Taken together, these results suggested that the overall SBIR/STTR applicant pool may prove to be a useful target group for further education about the NIH pediatric inclusion policy.

The review of the NIH pediatric inclusion policy demonstrated that simply including children in clinical research is not sufficient to ensure that this research will produce age-specific data. Unlike the NIH policy on the inclusion of women and minorities, the NIH policy on the inclusion of children does not include any requirement for the analysis of data by

[23] For example, see William Gerin, 2006. Writing the NIH Grant Proposal: a Step by Step Guide, Sage Publications.

age. Only about half of the grants that included children incorporated a plan for analyzing data by the age of the subjects.

The NIH study sections identified only a small number of grants as being "unacceptable" under the NIH pediatric inclusion policy. For the NICHD applications, study sections were most concerned with identifying the ages of the subjects and ensuring that justifications were provided if children were excluded.

Taken as a whole, these findings suggest that the majority of NICHD grantees are including children as research subjects, and study sections have identified only a very small number of compliance issues. However, the percentage of grants that included only children over 18, and the apparent confusion of reviewers and applicants about the definition of children, suggest that further education of the applicant and review communities about the NIH policy may be appropriate. In addition, the number of applicants who did not propose to analyze their data by age suggests that further education of applicants and scientists about the goals of the policy and the benefits of including children in research studies may be helpful. In particular, the results suggest that the small business and technology transfer communities could especially benefit from these types of efforts.