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Inclusion of Women, Minorities, and Children in Clinical Trials: Opinions of Research Ethics Board Administrators

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Abstract

IN AN ATTEMPT TO ENCOURAGE INCLUSION of women, minorities, and children in clinical trials, the U.S. National Institutes of Health (NIH) requires investigators conducting NIH-sponsored research to adequately address NIH inclusion guidelines concerning recruitment of women, minorities, and children. A survey of U.S. Research Ethics Board (REB) administrators at institutions receiving NIH funding indicated awareness and implementation of the inclusion guidelines. According to the administrators, investigators and REBs address inclusion in more than half of the relevant protocols. About half of the REB administrators consider the guidelines partly responsible for increased attention to inclusion, but only about a quarter believe that there is greater inclusion as a result.

Keywords

National Institutes of Health; Research Ethics Board administrators; inclusion policy; justice

ACCORDING TO THE NIH INCLUSION guidelines, principal investigators (PI) are to propose their plans for the inclusion of women, minorities, and children in their research proposals or justify their exclusion (National Institutes of Health, 1997; National Institutes of Health, 1998; National Institutes of Health, 2001). The NIH inclusion guidelines were adopted to increase the representation of women, minorities, and children in clinical research in order to address potential harms (real and perceived) created by their exclusion or omission. For example, female and pediatric patients can be harmed as a result of the exclusion of women and children from research when their physician is forced to prescribe to them a drug that has been tested only in male subjects. Members of minority groups can be harmed if enrollment in research is perceived as a benefit and members of minority groups are routinely excluded from access to this benefit.

It is the responsibility of Research Ethics Boards (REBs), scientific review groups (SRGs), and NIH program staff to evaluate whether the PI has adequately addressed the inclusion of women, minorities, and children and/or the adequacy of their justification for the exclusion of any or all of these populations (National Institutes of Health, 1997; National Institutes of Health, 1998; National Institutes of Health, 2001). Specifically, REBs are instructed to make sure that NIH-sponsored investigators provide adequate details on the composition of their study populations and appropriate justification for the exclusion of any particular sub-population (National Institutes of Health, 1997; National Institutes of Health, 1998; National Institutes of Health, 2001). Prior studies have assessed the opinions and attitudes of PIs and

SRGs on the NIH guidelines but no study has examined the views and experiences of REB administrators (Corbie-Smith, Durant, & St. George, 2006; Taylor, 2008).

Background

History

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research produced the Belmont Report, which set out three basic principles to guide the conduct of human subject research: respect for persons, beneficence, and justice (National Commission for the Protection of Human Subjects, 1979). The principle of justice as articulated in the Belmont Report is primarily concerned with the protection of vulnerable populations from exploitation. In the wake of AIDS patients' demands for access to experimental therapy, empirical evidence that research participation was less risky than assumed, and attention from women's health activists, the principle of justice was used to support a shift from protecting individual subjects (especially those considered vulnerable) to assuring the equitable access to the benefits of research (Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies, 1994; Mastroianni & Kahn, 2001).

Inclusion Guidelines

Attempts by the federal government to encourage the inclusion of women in clinical research began in 1985 when the NIH Women's Advisory Committee recommended that all NIH applicants include women in their clinical research, or justify their exclusion (Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies, 1994; Marshall, 2005). In 1990, the Government Accounting Office (GAO) noted that NIH had made little progress in implementing the Advisory Committee's recommendations (U.S. General Accounting Office, 1990). In response to the GAO report, the NIH and Alcohol and Drug Abuse and Mental Health Administration adopted guidelines stating that women should be included in research (Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies, 1994). No formal accounting of the impact of these guidelines was conducted (Levine, 1996). The US Congress strengthened these guidelines by mandating the inclusion of women and minorities in clinical research conducted by the NIH in the NIH Revitalization Act of 1993 (Public Law 103-43, 1993). The guidelines apply to all biomedical and behavioral research sponsored by the NIH with particular attention to Phase III clinical trials (National Institutes of Health, 2001). The NIH released "The NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research," mandating the inclusion of women and minorities in clinical research in 1994 (National Institutes of Health, 1994; National Institutes of Health, 2001).

Congressional hearings in 1995 included results of a review of NIH-supported research conducted by the National Institute of Child Health and Human Development and the American Academy of Pediatrics, which concluded that 10–20% of projects "inappropriately excluded children" (National Institutes of Health, 1998). In March 1998, the NIH released "Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" (National Institutes of Health, 1998). The guidelines are very similar to those mandating inclusion of women and minorities, and were motivated by similar concerns about harms of exclusion. PIs submitting research proposals to NIH must include children in their study populations or justify their exclusion (National Institutes of Health, 1998).

Implementation

It is important to note that the adoption of these guidelines to include women in clinical research was not uniformly supported at the time and the utility of the minority guidelines continue to

be an active topic of debate (Wolf, 2006; Duster, 2006; Cho, 2006; Bhopal, 2006; Foster, 2006; Brewer, 2006; Cohn, 2006; Bloche, 2006). At the time the women and minority guideline was adopted, the journal *Controlled Clinical Trials* (now *Clinical Trials*) published an issue on the guidelines. The first article was authored by a group of investigators engaged in clinical research affiliated with the NIH, followed by a number of articles in response (Freedman et al, 1995). Some argued that the underlying premise that women had been systematically excluded from trial participation was false (Piantadosi, 1995; and later Meinert, Gilpin, Ünalp, & Dawson, 2000). Others argued that the requirement for the “appropriate representation” minority groups in study populations was both vague and impractical and such a goal supported the false premise that only research that included specified proportions of minority group members would be generalizable to the population (Buist & Greenlick, 1995; Meinert, 1995; Piantadosi, 1995; Woolson et al., 1995). Still others noted that efforts to increase the number of minority group members in clinical research supported the notion that race was a biologic rather than social construct (Brawley, 1995).

It is not clear whether these and other scientific arguments were discounted or disregarded. More recent commentary has highlighted the fact that emphasis on labeling and counting research subjects is not enough to guarantee that enough women and minority subjects are included to conduct valid data analysis (Vastag, 2003). Others note that the lack of clarity regarding the definitions of minority groups and a failure to provide guidance to investigators regarding “appropriate inclusion”—to test hypotheses, to generate hypotheses, or equitable distribution of risks and benefits—limit the effective implementation of the guidelines (Corbie-Smith, Miller, & Ransohoff, 2004; Rathore & Krumholz, 2003).

As designated in the guidelines, REBs, NIH scientific review groups, and NIH program staff all have responsibility for the evaluation of principal investigators’ adherence to the inclusion guidelines (National Institutes of Health, 1997; National Institutes of Health, 1998; National Institutes of Health, 2001). REBs have a critical role in both protecting the welfare of human subjects and implementing national, state, and local policy regarding the conduct of human subject research. The purpose of this survey was to assess the experience and attitudes of REB administrators about the implementation of these justice-based policy recommendations.

Methods

Sample

A total of 712 REB administrators affiliated with U.S. institutions (schools of medicine, research institutes, independent hospitals, etc.) that conducted human subject research projects sponsored by the NIH during fiscal year 2000 were considered eligible for enrollment. In order to generate a sample large enough to compare groups of respondents, as well as for financial and logistic reasons, a random sample of half of the institutions ($n = 306$) was created using STATA (StataCorp LP, 2001). Complete mailing addresses for REB administrators affiliated with each site were collected via a comprehensive web search (e.g. Google and/or institutional websites) or by phone. All eligible REB administrators were mailed a letter describing the study and a hard copy of the questionnaire. The first mailing was sent in January 2002. Two weeks after the first survey package was sent, a reminder postcard was sent to all non-responders. Four weeks after the original mailing, a second mailing was sent with a letter and a copy of the survey (Dillman, 2000). REB administrators were asked to complete the surveys themselves or to forward the survey to the member of their REB or REB staff most familiar with their REB’s implementation of the inclusion guidelines. Each subject was given a unique identifier in order to track and follow-up with non-responders.

Survey

Survey domains and questions were developed based on documents that detail REB responsibilities regarding the implementation of the NIH Guidelines (National Institutes of Health, 1997; National Institutes of Health, 1998; National Institutes of Health, 2001). Drafts of the survey were reviewed by an expert in survey design and with local REB administrators. Survey domains included: REB experience with implementation NIH guidelines, opinions regarding the effectiveness of the guidelines, types of justifications proposed for the exclusion of groups of potential research subjects at their institution, basic details about the respondent's training and REB service, and basic demographic information.

Analysis

Data from returned surveys were entered into an Excel database and later uploaded into STATA, version 7.0, statistical software for univariate and bivariate analysis (StataCorp LP, 2001). A number of questions required respondents to indicate whether they "strongly agree, agree, neither agree nor disagree, disagree or strongly disagree" with statements about the effectiveness of the NIH guidelines. Based on the characteristics of the variable distributions, these responses were collapsed such that those who were neutral, disagreed, or strongly disagreed were combined and compared with those who strongly agreed or agreed.

Results

Surveys were sent to 306 eligible respondents. Twenty-eight respondents returned blank surveys indicating that their institution had no experience with the inclusion guidelines. One hundred and ten completed surveys were returned. The response rate was 39% (110/278).

Respondent Demographics and Background Characteristics

A summary of relevant respondent demographics and characteristics as well as the REB with which they were affiliated is provided in Tables 1 and 2. Respondents affiliated with schools of medicine and research institutes were more likely to respond than their colleagues affiliated with schools of arts and sciences and other institutions that conduct human subject research. Forty percent of the respondents indicated that their REBs reviewed over 300 new research proposals in the previous year. Respondents affiliated with REBs at schools of medicine were more likely to report reviewing more than 300 proposals a year ($p = .002$).

Almost two-thirds (63%) of the respondents indicated that less than 50% of the research reviewed by their REB is sponsored by the federal government. Respondents affiliated with REBs at research institutes were less likely to report that they reviewed more than 300 proposals in the last year ($p = .002$) and more likely to report that more than fifty percent of the proposals in their research portfolio were federally funded ($p = .000$). Sixty-seven percent of respondents reported that their REBs spent less than 30 minutes on the initial review of each new proposal.

Attitudes, Beliefs, and Opinions about Inclusion Guidelines

Almost all respondents indicated their REB had experience with implementing the women, minority, and children guidelines and very few (2–3%) indicated they had a negative experience with either set of guidelines. Table 3 displays the respondent level of agreement with attitudes, beliefs, and opinions about the inclusion guidelines. In general, respondents indicated similar levels of agreement with each statement about the women and minority guidelines as compared to their agreement with each statement about the children guidelines. The one statistically significant difference found was between those who indicated that investigators consistently address the inclusion of children as compared to the inclusion of women and minorities in their

research proposals. A number of respondent or institutional characteristics predicted a higher level of agreement with different statements.

- Administrators affiliated with a medical school and/or an institution that reviewed a high volume of research proposals were more likely to agree that inclusion of women, minorities, and children was a frequent topic of discussion at their REB.
- Administrators affiliated with institutions where more than 50% of their research is federally funded were more likely to agree that PIs at their institutions addressed the requirements of the guidelines in their research proposals.
- Administrators who had *not* taken an ethics course were more likely to agree that the guidelines are in part responsible for their REB's attention to the inclusion of women and minorities. Administrators affiliated with a high-volume institution were more likely to agree that the guidelines are in part responsible for their REB's attention to the inclusion of children.
- While relatively few administrators indicated they believed that the number of women, minorities, and children enrolled in research at their institution had increased as a result of their REB's attention to the inclusion guidelines, administrators at high-volume institutions were more likely to agree that the number of children enrolled in research at their institution had increased as a result of their attention.
- Administrators who had taken an ethics course were more likely to indicate that NIH guidance on the women and minority guidelines were adequate. Administrators affiliated with a medical school and who have taken an ethics course were more likely to agree that NIH guidance on the guidelines on the inclusion of children were adequate.

Reasons for Exclusion

According to the NIH inclusion guidelines, there are certain circumstances under which it is acceptable to exclude women, minorities, or children from a clinical trial (National Institutes of Health, 1998; National Institutes of Health, 2001). Respondents who indicated that their REB had experience with the implementation of the inclusion guidelines were first asked if they had reviewed a proposal in the last year that proposed the inclusion of men *or* women only ($n = 87$); members of one *or* a limited number of racial/ethnic groups ($n = 58$); or the inclusion of adults only ($n = 94$). The reasons considered "appropriate" by the NIH were provided verbatim in the survey instrument. Respondents were asked whether or not each "acceptable" reason was provided in any proposal they reviewed and then asked identify the most common reason used in the past year (Table 4). The "research question addressed is relevant to" males or females, one racial/ethnic group or a limited number of racial/ethnic groups or sub-groups, or adults was the most common reason for the exclusion of one gender (80%), racial/ethnic subgroup(s) (70%), or children (57%). Of note, the inclusion of a single racial/ethnic group or limited number of racial/ethnic subgroups "to fill a research gap" (20%) was the second most common reason among those listed to justify limits on the inclusion based on minority status.

Discussion

While respondents agree that the topic of inclusion of women, minorities, and children is often discussed by their Boards, from their vantage point, their attention to the guidelines has not led to an increase in the number of women, minorities, and children enrolled in research conducted at their institutions. On the one hand, this is understandable as the goal of the guidelines is to increase the number of women, minorities, and children at the national level. That is, small increases at the local level may not be obvious to those engaged in the review

and approval of human subject research. On the other hand, only attention at the local level will result in demonstrable increases at the national level. It is also the case that REBs are not given authority to penalize NIH-sponsored research proposals that fail to address adequate inclusion. It is the SRG that has the authority to designate a protocol as out of compliance with the guidelines and therefore subject to the additional of points to the overall score given to the protocol. Giving the responsibility of penalizing non-compliance to a body meant to represent a government agency is preferable to giving this responsibility to local REBs that are known to vary in their implementation of federal guidelines.

Little empirical research has been conducted on the attitudes and opinions of the individuals and groups responsible for the implementation of the NIH guidelines. That said, comparisons can be made among the responses by SRG members, PIs, and REB administrators. Compared with a similar survey of NIH SRG members, REB administrators are less likely to agree that the inclusion guidelines have resulted in an increase in the number of women and minorities enrolled in clinical research (Taylor, 2008). Taylor found that more than half of SRG members responding indicated that the guidelines had resulted in an increase in women (54%) and minorities (56%) in research and less than a third of SRG members (30%) agreed that the guidelines had resulted in an increase in the number of children included. REB administrators are also less likely than PIs to agree that the NIH guidelines have influenced the inclusion of women and minorities (Corbie-Smith, Durant, and St. George, 2006). Corbie-Smith, Durant, and St. George (2006) found in their survey of National Heart, Lung and Blood Institute (NHLBI)-funded principal investigators that 69% agreed that the inclusion guidelines had been successful in increasing gender diversity and 55% agreed the guidelines had been successful in increasing the number of minorities enrolled in clinical trials. Of note, REB respondents to this survey indicated that PIs were more likely to address the inclusion of children in their research as compared to the inclusion of women and minorities. This may be related to the fact that the inclusion guidelines regarding children were introduced more recently or the inclusion of children is more easily addressed—that is, it is likely clear to both PIs and REBs when it is appropriate to exclude children. This hypothesis is supported by the fact that almost all ($n = 94$) of the respondents had reviewed and approved study in the past year that included adults only. That is, the exclusion of children appears to be more common than the exclusion of one gender or one more racial/ethnic group and the reasons for exclusion are more justifiable (e.g., there are laws or regulations that bar their inclusion).

The most common response among administrators regarding their experience with PI justifications for the exclusion of a population or sub-populations of potential subjects was that the study under review was designed to address a research question relevant to only one sub-population. Administrators were asked only if they had reviewed an application that included a justification, not how often they encountered proposals that proposed to exclude particular subjects. An estimate of incidence may indicate how often the guidelines are considered or referred to in the process of a review. It would also be interesting to find out whether administrators recall their REB reviewing a justification and concluding it to be inadequate and returned to the responsible PI.

This study has a number of limitations. The survey had a relatively low response rate (39%). In a review of response rates from other self-administered surveys of Institutional Review Board (IRB) administrators in the U.S., a response rate of 39% was found to be within the range of 22% to 68% reported in the literature (22% [White & Gamm, 2002]; 36% [Weise et al., 2002]; 54% [Jones et al., 1996]; 68% [Kodish et al., 1992]). The literature indicates that response rates are higher (83–98%) when surveys of IRBs are conducted over the phone (83% [Ernst et al., 2005]; 84% [Whittle et al., 2004]; 98% [DeVries & Forsberg, 2002]). Another limitation is that the results depend on the self-reporting of the respondents. While efforts were made to encourage respondents to be candid, their responses may have been influenced by an

interest on their part to portray their institution as successful in their attention to the guidelines. In addition, some questions on the survey asked respondents to consider events in the past and are therefore influenced by recall bias. Related to both self-report and recall bias, this project did not include the review of actual proposals submitted to and reviewed by individual REBs.

Conclusion

The results of this survey indicate that REB administrators affiliated with REBs that review NIH-sponsored research proposals are aware of, and have experience with the NIH inclusion guidelines. Based on this survey, the implementation of the inclusion guidelines could be regarded as a success from the perspective of REB administrators, because they rate their implementation experience as relatively positive. As a proxy measure of success, more than half of the REB administrators surveyed believe that PIs responsible for protocols submitted to their REB adequately address the inclusion guidelines. It is possible that PIs that have applied for or received NIH funds are more likely to address the guidelines than those PIs with funds from other sources. This hypothesis could not be tested as REBs were not asked whether NIH-funded PIs were more likely than PIs funded by other sources to include women, minorities, and children, but this question could be tested in future research.

Research Agenda

Given that few respondents agreed that attention to the NIH guidelines has improved the representation of women, minorities, and children in research conducted at their institution, it would be interesting to find out whether REB administrators believe that the NIH inclusion guidelines were therefore unsuccessful on this point, whether they believed the diversity of research subjects in their study populations were adequate prior to the implementation of the guidelines, or whether they have suggestions about how to better accomplish the goal of achieving greater diversity of research subject populations. In their initial review of research proposals, REBs can only assess what the PI has planned in terms of subject recruitment. Future research ought to explore whether, in their review of annual reviews and annual reports, REB administrators and NIH program officers find that PIs meet their recruitment goals.

In order to fully evaluate the impact of the NIH guidelines on PI, REB, and SRG behavior, a comprehensive review of the lifecycle of a number of NIH-sponsored research proposals could be conducted. However, such a study would rely on the willingness of PIs to share the relevant documents. The initial application could be retrieved through a FOI request to NIH but the documents submitted to, and correspondence from the responsible REB and SRG review would need to be provided directly by the PI. If made available, a review of the documents may reveal details about the attention that the PI, REB, and SRG paid to the guidelines. NIH program officers would also be an appropriate source for a top-down view of whether the NIH guidelines have led to an increase in the enrollment of women, minorities, and children in aggregate.

Another approach to evaluating the effect of the guidelines on PI, REB, and SRG behavior would be to conduct in-depth interviews on topics of interest revealed by the two quantitative surveys conducted to date (Corbie-Smith, Durant, & St. George, 2006; Taylor, 2008). In-depth interviews may reveal opinions and attitudes not considered by those designing the surveys. In reference to the work of REBs, one particular interest would be to find out more about how REB administrators consider the NIH guidelines as it relates to their regulatory requirement to assess whether the selection of subjects is equitable. One potential line of questioning could be whether REBs routinely refer to the NIH guidelines only when they are reviewing NIH-sponsored research or whether their familiarity with the guidelines leads them to assess the recruitment plans of all proposals more carefully.

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Biography

Author's Biographical Sketch

Holly A. Taylor is Assistant Professor in the Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health (JHSPH), and a Core Faculty member of the Johns Hopkins Berman Institute of Bioethics. She currently serves as Associate Director for Empirical Research in the Berman Institute of Bioethics. Dr. Taylor's primary interest is in the local implementation of federal regulations regarding the ethical conduct of human subject research. In particular, she is interested in the process by which potential subjects are identified and recruited to participate in research and methods to improve the process of informed consent. Dr. Taylor is also interested in the REB decisionmaking process, specifically whether and how the group identifies and considers ethical issues related to the proposals they review. She is also currently engaged in a project on decisions made by public health investigators regarding the provision of ancillary care to their research subjects.

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TABLE 1
Respondent Demographic Characteristics, Role and Experience ($n = 110$)

Sex	
Female	71%
Race	
White	88%
African American	6%
Asian/Pacific Islander	5%
Other	1%
IRB Administrator	72%
IRB Chair/Co-chair	14%
IRB Staff/Other	14%
Personal Experience with Conducting Research	58%
Attended IRB-related Continuing Education Course	91%
Completed an Ethics Course	67%

TABLE 2
REB Characteristics ($n = 110$)

Type of Institution *	
Medicine	54%
Research Institute	15%
Arts and Sciences	15%
Hospital	10%
Public Health	1%
Other	10%
New Proposals Reviewed Annually	
<120	32%
121-300	28%
>300	40%
Percentage of Trials in Portfolio Supported with Federal Funds ($n = 109$)	
<50%	63%
>50%	33%
Time Spent on Initial Review of Proposal	
<30 minutes	67%
>30 minutes	33%

* Terms used are those used by OER to categorize institutions.

TABLE 3
IRB Administrator Agreement with Statement about NIH Guidelines

Statement about NIH Guidelines	Type of Guideline		P-value
	Gender/Minority	Children	
Inclusion frequent topic of discussion at IRB meetings	45 (47%)	60 (60%)	.06
Investigators whose grant applications are reviewed by their IRB consistently address inclusion	49 (53%)	69 (69%)	*.02
Guidelines in part responsible for amount of attention given by IRB in reference to inclusion	51 (60%)	59 (59%)	.88
The number of women, minorities, and children has increased as a result of IRB compliance with NIH guidelines	26 (28%)	19 (19%)	.13
Guidance from the NIH has been adequate	43 (46%)	49 (49%)	.67
Total	94 (100%)	100 (100%)	

TABLE 4

Reasons Used for Exclusion of Group(s) of Subjects

Reason used for Exclusion	Group Excluded		
	Males or Females (n = 94)	One or More Racial/Ethnic Group(s) (n = 94)	Children (n = 100)
The research question addressed is relevant to only one group.	98%	93%	97%
Inclusion too risky.	45%	9%	56%
Evidence from prior research strongly demonstrates no difference between groups.	12%	18%	n/a
Sufficient data already exist with regard to outcome of comparable studies in the excluded group, and duplication is not needed in this study.	20%	19%	n/a
Group representation of specimens or existing databases cannot be accurately determined and this does not compromise the scientific objectives of the research.	38%	32%	n/a
One group is excluded or inclusion is severely limited because the purpose or method of the research constrains the investigator's selection of study subjects.	41%	28%	n/a
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.	33%	n/a	60%
Some racial/ethnic groups or sub-groups are poorly represented because the geographical location of the study has only limited numbers of these racial/ethnic groups who would be eligible for the study.	n/a	38%	n/a
A single racial/ethnic group is proposed to fill a research gap.	n/a	71%	n/a
Laws or regulations barring inclusion of children in the research (e.g., Subpart D of 45 CFR 46, limiting risk to which children can be exposed).	n/a	n/a	59%
A separate age-specific study in only children is warranted and preferable (e.g., relative rarity of disease in children or network of pediatric trial sites already in place to conduct research).	n/a	n/a	51%
Other studies underway that address the same research question in children.	n/a	n/a	35%