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A Reappraisal of Female Adolescent Participation in Drug Clinical Trials

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This paper presents an analysis of the concept of acceptable birth control inclusion/exclusion criteria for female adolescents in pharmaceutical clinical trials. The analysis calls attention to the need to examine the exclusion of adolescents who are abstinent and the definition of acceptable birth control, as well as the potentially negative impact of the application of this definition on both individual adolescents and on research study data. This analysis is guided by ethical principles elucidated in the Belmont Report[1] and regulations and policies outlined in the Department of Health and Human Services (45 CFR 46). Three ethical principles are to be used to inform the IRB decisionmaking process: (a) respect for persons, (b) beneficence, and (c) justice. Adolescent psychological/social/sexual development and issues regarding adolescent sexuality will also be addressed. Inclusion criteria for a phase III clinical trial will be used to provide an example of ethical issues that arise.

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Special Considerations for Children Involved as Subjects in Research

DHHS regulations (45 CFR 46, Subpart D) provide for "Additional Protections for Children Involved as Subjects in Research." This section of the federal regulations provides IRBs with guidelines for additional considerations that recognize the special vulnerability of children. These regulations require that procedures and interventions be classified into 1 of 4 categories, with each based on the degree of risk and benefit to individual subjects. The following case study falls into the category of studies that involve greater than minimal risk but have the potential to directly benefit the individual subject. The DHHS regulations instruct IRBs not only to weigh the potential risks and benefits of such studies, but also to assure that provisions are made to obtain assent from minor subjects and permission of their parent(s) or guardian(s). A brief description of the case study is presented.

Case Study

Overview of Study. Clinical trial inclusion and exclusion criteria used in this analysis describe the sample for a Phase III, double blind trial of an inhaled drug for treatment of asthma that afflicts all age groups but has higher morbidity and mortality rates in adolescents compared to all other age groups. The research sample and inclusion/exclusion criteria included males and females ages 12 and up. The trial compared a new, investigational drug with a drug considered standard treatment for the chronic condition. In previous preliminary studies the investigational drug, which had a chemical structure similar to the standard treatment drug, demonstrated improved clinical efficacy with significantly fewer side effects than standard treatment.

The investigators proposed recruitment of subjects from physician practices as well as through IRB-approved advertising in local publications. Participants were to be provided with the study medication for 14 weeks of therapy. Follow-up visits to monitor clinical efficacy and adverse effects would occur at the physician's office 9 times during the study at no cost to participants. A modest cash payment would be given to study participants to offset costs of transportation and time lost from school or work.

Inclusion/Exclusion Criteria. Individuals of at least 12 years of age who presented with clinical evidence of moderately severe symptoms requiring use of the "standard treatment" drug were considered

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Background

Recently, a great deal of attention in both the popular media and the scientific community has been focused on adolescents and the troubling increases in rates of disease, injury, violence, and death in this population.[1-9] The Healthy People 2000 objectives for the nation identify risk behaviors as a major threat to adolescent health.[10] It is acknowledged that much more research is needed to elucidate the factors that contribute to adolescent risk, understand how disease or trauma may affect youth differently from children or adults, and develop appropriate and effective interventions. For this research to be successfully conducted, adolescents must be willing to participate and provide accurate information. This often means assuring adolescents that the information they share about risk behaviors will be kept confidential. Satisfying this request derives from the ethical requirement to respect individual autonomy by acknowledging the growing capacity of the adolescent for self-determination. A recent review article by Weir and Peters examines the expanding body of research, experience, and expert judgment supporting the capacity of adolescents, with some exceptions, to make major health decisions and to give informed consent, whether in clinical or research settings.[11] Moreover, the law frequently has recognized this capacity by allowing minors to give their own consent for specific health care services.[12]

At the same time, adolescents sometimes are protected under the law as minor children who may be vulnerable to exploitation because of their age and status. Some of these protections have had the unintended effect of limiting the participation of adolescents in research. The tension between a need for confidential yet informed participation and protection from exploitation requires that careful, balanced consideration be given to issues of parental involvement in informed consent when adolescents are included in research studies. Federal regulations give considerable authority to institutional review boards to determine the subject safeguards required in any proposed research study because these regulations have always been intended to protect where protection is needed but never to be so inflexibly applied as to impede access to research participation.

In 1994 Mammel and Kaplan surveyed 183 nationally distributed IRBs.[13] Their data demonstrated that 70% of their responding IRBs require parental permission for *all* research on minors. In fact, slightly more than half would require parental permission to conduct a simple satisfaction questionnaire for minor subjects. There was considerable support among respondents for changing federal regulations to permit adolescent consent for anonymous surveys, sensitive material surveys, venipuncture, and research on disease for which minors have the legal right to consent to diagnosis and treatment. This is a puzzling finding since these IRBs operate within a uniform set of regulations that confer substantial local authority to waive parental permission in every situation to which they responded (45 CFR 46.408(c)). Investigators studying adolescent health also noted a wide diversity in reported understanding, practice, and attitudes among IRBs reviewing research proposals focused on adolescent subjects. As a result of increasing attention to the issue,[14-16] in 1995 the Society for Adolescent Medicine endorsed guidelines for adolescent participation in research.[17] The guidelines were intended to educate IRBs on issues in adolescent research and to promote a more balanced interpretation of the regulations. The guidelines encourage IRBs to more actively consider waiving the parental permission requirement when research presents only minimal risk, adequate subject protection is in place, and applicable law authorizes minor consent for diagnosis and treatment of conditions under study.

Shortly after the guidelines were issued, the Adolescent Medicine HIV/AIDS Research Network launched a multicenter observational study of HIV-infected youth. Obtaining IRB clearance for this study at 11 sites afforded an opportunity to examine the practices of 11 different IRBs reviewing one common study protocol recruiting minor adolescents. We report our experience here.

Methods

The REACH (Reaching for Excellence in Adolescent Care and Health) project of the Adolescent Medicine HIV/AIDS Research Network is a multicenter study enrolling HIV-positive youth ages 12 to 18 years, infected through sex or drug use, into an observational study of HIV disease progression and STD comorbidity, using a control group of high risk youth. The study has been described in detail elsewhere.[15] REACH has one common protocol, requiring quarterly visits, that compiles information through a direct interview on clinical status and service utilization; a

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computerized interview for drug use and sexual behavior; the collection of blood, urine, and genital tract secretions for immunologic and virologic measurement; assessment of bone age through wrist radiologic examination; centralized urine drug screening; and physical examination including STD screens and cervicography (Table 1). Data entered by the subject in the computerized interview are identified by unique subject code, encrypted immediately, downloaded at the site, and sent to a central data operations office to be merged into an identifier-stripped database. The data are not available to the staff at the site. Subject urine is collected locally for screening for illegal drugs and sent to a central testing laboratory. Results are sent directly to the data operations office; the site does not receive the test results. All REACH sites have certificates of confidentiality from the federal government. The blood volume required by the protocol is approximately 100 ml at baseline and annually, 60 ml at three and six months, and 80 mls at six months for HIV-positive subjects; and approximately 60 ml at baseline and annually and 50 mls at six months for HIV-negative subjects. There is no venipuncture for HIV-negative subjects at three and nine months.

A common study protocol and sample consent forms were written and provided to each of the sites for use in preparing their individual IRB submissions. Several months after the last site received approval in 1996, all IRB notification letters were reviewed, and investigators were queried about their experiences in submitting the protocol by one interviewer (ASR) using a short survey form. Questions were designed to collect information about the volume of adolescent research reviewed by the IRB, the IRB's assessment of the level of risk the REACH protocol presented, whether a waiver of parental permission was sought and obtained, investigator perceptions of what factors influenced IRB decisions, whether the IRB permitted investigators to attend the review session, and whether protocol changes had been required. Investigator responses were accepted for all survey items. If the investigator was unaware of the volume of adolescent research submission to the IRB, this information was obtained from the IRB coordinator at the site by the interviewer. Provisions of local law governing minor consent for health services were verified by one of the authors (AE).

Table 1. List of Measures Obtained in the REACH Study Protocol (schedule frequency varies)

Face to Face Interview
demographic history
health history
suicidal ideation
Interactive Computerized Interview (ICI)
ICI results not available to site staff
social support
depression
life change events
HIV disclosure
coping
anxiety
sexual and drug-related behaviors
Laboratory
blood for hormonal, immunologic, virologic, and serologic studies (depending on the schedule, HIV-positive subjects: 60-100 ml, and HIV-negative: 50-65 ml)
urine for pregnancy tests, virology studies, and illegal drug screens
drug screen results not available to the site

Physical Examination
height and weight
Tanner staging of sexual maturity
skin-fold thickness —triceps, subscapular, and suprailiac regions —mid-arm circumference
in depth skin and oral examination
gynecologic and urogenital examination with swab collection
cervicography (Cervigram National Testing Laboratories, Fenton, MO) pictorial technology and computerized mapping of cervical ectopy
annual tuberculin testing
delayed-type hypersensitivity skin test assessment for HIV-positive subjects using three antigens, one of which is under IND
radiologic examination of wrist to determine bone age annually until closure

Results

Eleven of the current 15 REACH sites were active in 1996, submitted the first study protocol to their local IRBs, and are represented in this survey. Four of these are from the southeastern United States, three from the mid-Atlantic states, two from the Northeast, and one each from the Midwest and West Coast (Table 2). The majority (73%) of the sites' IRBs were reviewing an adolescent-focused study protocol three to four times per year.

Four IRBs did not consider that the protocol represented greater than minimal risk for subjects, while one judged it to be greater. One other judged it to be greater than minimal risk for HIV-negative controls only. Two required changes in order to consider it not greater than minimal risk: one imposed a screen for anemia prior to blood draws and the other required that the wrist x-ray for HIV-negative controls be deleted (as it posed a risk with no research benefit as a condition for waiver of parental permission). Three IRBs gave no indication to the investigator that the issue of greater than minimal risk had been discussed; in two of these situations, the investigator had not asked for a waiver of parental permission, but in the third, some interaction on study risk would have been expected since the waiver was requested and denied.

In all but one study state, the age of majority is 18 years and parental permission was not obtained for 18-year-old subjects who were adults under state law. Eight of 11 investigators requested some type of waiver of parental permis-

sion for minors; the three who did not were all from the South (sites 2,3,4). Of the eight who requested a waiver, five asked for unqualified waivers (sites 1,5,6,7,9), and three others (sites 8,10,11) qualified the waiver by requesting it for HIV-positive youth only. Two of the five investigators requesting unqualified waivers were denied (sites 5,9); one other (site 6) was permitted a waiver for specific categories, namely legally emancipated minors, minors not living at home and without home contact for over 6 months, and HIV-positive youth with undisclosed serostatus. Another was granted a waiver (site 7) for both HIV-positive and HIV-negative subjects only after wrist radiologic examination was deleted for HIV-negative subjects; and the last (site 1) was granted a waiver to be decided on a case-by-case basis by the investigator and an IRB coordinator. Two of the three sites requesting qualified waivers only for HIV-positive subjects were granted the waiver. In the third case, the IRB extended the waiver to include the HIV-negative subjects, citing the potential benefit to be realized by high risk youth participating in this protocol.

We asked investigators their impressions of the factors that influenced IRB decisions related to waivers. Only one investigator (site 5) believed that the waiver request was denied specifically on the basis of subject risk; this IRB was the only one to judge the protocol to be greater than minimal risk and did not propose changes that could mitigate that observed risk. Two investigators (sites 2,6) stated that the IRB perceived legal prohibitions to granting the waiver, although adolescents are able to access health care for STDs/HIV disease in every REACH site jurisdiction, a factor specifically stated in the federal regulations (45 CFR 46.402(a)). Three investigators (sites 3,4,6) believed the decisions of their IRBs were disproportionately driven by risk aversion. Seven of the investigators (64%) believed that simple IRB precedent based on their past decisions was a deciding factor. Only three of the 11 investigators were present during the IRB deliberations.

Table 2. Institutional Review Board Characteristics, Decisions, and Their Rationale as Perceived by Submitting Investigators

	SITES										
FACTORS	1	2	3	4	5	6	7	8	9	10	11
Geographic Region	SE	SE	SE	SE	MA	MA	MA	NE	NE	MW	WC
Adolescent Research Volume	H	M	M	L	M	M	M	M	M	L	M
Study Considered Not Greater than Minimal Risk Research	yes	unk	yes	unk	no	yes[1]	yes[2]	yes[3]	unk	yes	yes[4]
Parental Permission Waiver Requested	yes	no	no	no	yes	yes	yes	yes[5]	yes	yes[4]	yes[4]
Parental Permission Required	no[6]	both*	both*	both*	both*	both[7]*	no[8]	both[9]*	both*	no[10]	yes[11]
Decisions Perceived Due to											
• subject risk	unk*	no	no	no	yes	no[1]	yes	no[3]	no	unk*	yes
• institutional risk aversion	unk*	no	yes	yes	no	yes	no	no	no	unk*	no
• IRB past decision precedent	unk*	yes	yes	yes	yes	yes	no	yes	yes	unk*	yes
• local law prohibitions	unk*	yes	no	no	no	yes	no	no	no	unk*	no
Required Change in Protocol	no	no	no	no	no	no	yes[8]	yes[3]	no[12]	no	no
Investigator Invited to Attend	no	yes	no	no	yes	no	yes	no	no	no	no

Geographic Area: SE=Southeast; MA=Mid-Atlantic; NE=Northeast; MW=Midwest; WC=West Coast
*unk=unknown, both=required for both HIV positive and HIV negative subjects
Volume: H=Heavy (at least one submission per IRB session on average); M=Moderate (one submission every 2-3 sessions on average); L=Light (one submission every 4 or more IRB sessions on average).

Notes

[1] Considerable discussion and independent review by Radiation and Pharmacology/Therapeutics committees.
[2] Deletion of wrist x-ray for HIV-negative subjects made study protocol not greater than minimal risk.
[3] Required anemia blood screen prior to blood drawing was added.
[4] For HIV positive subjects only.
[5] For HIV positive subjects who have not disclosed serostatus to parents or guardians.
[6] If 14 years or older, waiver decided on a case-by-case basis between investigator and IRB coordinator.
[7] Waiver granted for legally emancipated minors not living at home and with no contact for more than 6 months, and HIV-positive subjects who have not disclosed.
[8] IRB required deletion of wrist x-ray for HIV negative subjects as a condition for waiver of parental permission.
[9] Waiver granted for HIV-positive subjects who have not disclosed serostatus to parents or guardians.
[10] Citing benefit from participation, IRB granted waiver for both HIV-positive and negative subjects although only HIV-positive waiver was requested.
[11] For HIV-negative subjects only.
[12] Investigator initially required to add local expertise but IRB reconsidered after letters of support were submitted.

Discussion

Because the determination that minimal risk not be exceeded is a critical factor in the decision to waive parental permission, an important question becomes, Does the REACH project study protocol constitute minimal risk research? The definition of minimal risk research in federal regulations states, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102(i)). We believed that the REACH protocol could be interpreted by individuals and institutional review boards as intrusive and/or intensive, but not as representing risk greater than that encountered within routine history and physical examination for sexually active youth.

Only four IRBs (sites 1,5,7,10) demonstrated internal consistency between risk judgment and granting parental permission waivers. Other IRBs (sites 6,8) accepted the study protocol as posing not more than minimal risk but granted qualified waivers based on emancipation or anticipated harm from seeking permission because it would require disclosure of serostatus. One IRB (site 11), when asked for a waiver for HIV-positive youth only, on the premise that the protocol was not greater than minimal risk for them but was greater than minimal risk for HIV-negative subjects, accepted the concept of two standards and granted the waiver. This last situation may be problematic because the assessment of risk is linked directly to the youth's HIV status. The definition of minimal risk was not meant to be conceived of as a sliding scale. Such thinking represents a slippery slope that could easily permit riskier research with disadvantaged subjects from dangerous neighborhoods.

There are, of course, other considerations an IRB must take into account in deciding to grant a waiver of parental permission. The regulations state that the requirement for parental permission can be waived if requiring parental permission is not a reasonable requirement for the conditions or populations involved in the research, if the waiver is not inconsistent with applicable law, and if an appropriate mechanism for the protection of subjects is substituted (45 CFR 46.408(c)). The choice of this mechanism depends on the nature of the study; the potential risks and benefits inherent in the study; and the age, maturity, status, and condition of the subjects. Only one IRB (site 1) specifically devised a strategy for taking these other factors into consideration.

Federal regulations define children not by any particular age range, but rather as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" (45 CFR 46.402(a)). Thus minors who legally can give their own consent for STD or HIV testing and treatment might not even be considered children under the federal regulations for the purposes of a study in which procedures related to HIV or STD testing or treatment are involved.[19] Every state in which there is a REACH clinical site has laws or regulations that permit minors to access either STD or HIV testing and management without parental permission. This means that the application of regulations governing children as research subjects in a blanket fashion to studies involving adolescent subjects may be questioned. At the very least, the legal right of minors to access treatment and management should strongly influence the IRB in making a determination to waive parental permission.

We believed that participation in REACH merited a waiver of the requirement for parental permission because the full array of measures included in the study was consistent with the types of services sexually active adolescents can legally access for HIV/STD diagnosis and treatment in every state in which there was a participating clinical site. Furthermore, we believed there were additional protections for subjects in that (1) all recruitment occurred within the context of health care delivery, (2) all sites had certificates of confidentiality, and (3) all sensitive data would be computer-encrypted at the site and unavailable to staff. Finally, we believed the characteristics of the REACH subject population (either as cases or controls) in general and of certain segments in particular, specifically young gay men who had not yet disclosed sexual orientation or HIV status to families, presented a compelling reason to consider the waiver of parental permission requirements. While the HIV serostatus of the subjects should not be a factor in deciding whether a study constitutes greater than minimal risk for subjects, it is entirely proper in our opinion for HIV serostatus and its implications to be considered in determining the nature of *appropriate* protection for subjects in research.

Conclusion and Recommendations

The review experience of this multicenter study demonstrates that the definition of minimal risk research by local IRBs is variable and not always consistent with the regulations. The perception of our investigators is that IRB decisions may frequently be based more on institutional risk aversion and precedent than on subject risk and adequate protection. We also note that in the first phases of their dissemination, the Society for Adolescent Medicine's Guidelines for Adolescent Participation in Research had little impact on IRB decisionmaking.

Given this, we believe that IRBs unfamiliar with the unique nature of adolescent care and research issues should add *ad hoc* reviewers (45 CFR 46.107(f)) who are familiar with adolescent health research in order to render a more judicious review of proposals for research with adolescent subjects. Additionally, the proposing investigator often should be encouraged to attend segments of IRB review

sessions. Such attendance would foster a fuller discussion of concerns and promote a collaborative solution to perceived subject safety considerations.

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UPDATE

Mandating Research with Children

More than a decade ago Bob Levine argued that as a matter of justice children should be included in research:

> If we consider the availability of a drug proved safe and effective through the devices of modern clinical pharmacology and clinical trials a benefit, then it is unjust to deprive classes of person, e.g., children . . . of this benefit.[1]

This year two policy initiatives—one at the National Institutes of Health and one at the Food and Drug Administration—seek to ensure that children will share in the benefits of research.[2]

On 1 October 1998 the NIH "Policy on the Inclusion of Children as Participants in Research Involving Humans" came into effect.[3] The policy stipulates that children must be included in NIH-conducted or -supported research involving humans, unless there are sound scientific and ethical reasons to exclude them. Examples of such reasons include: a research topic that is irrelevant to children; laws or regulations prohibiting the