Reducing Health Disparities and Enhancing the Responsible Conduct of Research Involving LGBT Youth

by Celia B. Fisher and Brian Mustanski

There has been a recent increase in public attention to health disparities in the incidence and treatment of mental health problems and sexual health risks among lesbian, gay, bisexual, and transgender youth. LGBT identification is a key risk factor for youth suicide attempts and substance abuse; young men who have sex with men and transgender women are at alarmingly high risk for HIV; and the sexually transmitted infection (STI) risk among women who have sex with women and transgender men is estimated to be at least as high as that among heterosexuals.[1] Although there is clearly a need for evidenced-based behavioral or biomedical prevention or treatment programs for suicide, substance abuse, and sexual health targeted to members of the LGBT population under the age of eighteen, few such programs exist, due in substantial part to limited research knowledge.[2]

Ambiguities in regulations that govern human subjects protections and the related inconsistencies in institutional review board (IRB) interpretations of regulatory language are the key reason for the lack of rigorous clinical trial evidence to support treatment choices and prevention approaches to reducing health disparities for this population. A major reason for these ambiguities is that ethical approval of research involving minors requires IRBs to apply both general rules for human subjects protections found under 45 CFR 46 subpart A (known as the "Common Rule") and specific rules for child participants under subpart D, "Additional Protections for Children Involved as Subjects in Research."[3] For example, although "minimal risk" is a key concept under subpart D regulations, the definition of "minimal risk" appears only in the Common Rule and does not distinguish how it should be applied to research involving adults and children. Given the socially sensitive nature of suicide, substance abuse, and HIV and STI research in general and LGBT research specifically, in the absence of empirical data to guide their decisions, IRBs must often rely on subjective judgments of minimal risk, which can lead to overestimation of the magnitude and probability of psychological, social, and informational harms that might arise from LGBT youth participation in clinical trials.

In addition, more than other youth, LGBT adolescents whose families are unaware of their sexual orientation or gender identity or whose families have victimized them on account of it may be reluctant to participate in studies that require guardian permission. This, in turn, intensifies problems of recruitment and unbiased sampling. However, many IRBs are reluctant to apply federal regulations permitting waiver of guardian permission under conditions in which such permission is clearly not "feasible" or "reasonable" to require. Consequently, many investigators have excluded LGBT individuals under eighteen years of age in health intervention research proposals because of anticipated or actual difficulties obtaining IRB approval. This situation is in conflict with current ethical discourse focusing on the right of youths to participate in trials that will protect them from receiving developmentally untested, inappropriate, and unsafe treatments. In this article, we describe these barriers and recommendations for providing LGBT youth safe and fair access to health research.

Overestimation of Research Risk

The Belmont principle of *beneficence*, which has been incorporated into national and international re-

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Requiring guardian permission can jeopardize the involvement of LGBT youth in research that could benefit them or their peers.

search ethics guidelines, obligates investigators and IRBs to ensure that research risks are minimized and benefits maximized. In U.S. human subjects regulations, research is considered "minimal risk" when "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 or psychological examinations or tests."[4] Appropriate application of the regulatory definition of "minimal risk" is a critical gateway to the approval of research involving minors. In the absence of empirical data and regulatory guidance on age-indexed examples of research risks, IRBs often overestimate potential harms of research involving children, and this is particularly the case for research on socially sensitive health behaviors among adolescents in general and LGBT youth in particular.[5] Thus, well-intentioned but value-laden and subjective evaluations of research harms that prevent research on LGBT youth are in conflict with the Belmont principle of *justice*, which requires that all populations have the opportunity to share in the equitable distribution of research risks and potential benefits.

For example, research involving LGBT youth is often classified as "greater" than minimal risk based on unsubstantiated assumptions that answering questions about mental health, sexual or gender identity, sexual risk, and related substance use behaviors has a high probability of producing significant psychosocial harms, increasing suicidality, influencing the trajectory of sexual orientation identity, or increasing the probability that adolescents will engage in behaviors that compromise health.[6] These assumptions persist despite evidence to the contrary from published studies on the attitudes toward suicide, substance abuse, and sexual health risks conducted with adolescents in general and LGBT youth specifically. Misapplication of the "greater than minimal risk" classification creates barriers for LGBT youth intervention research by requiring more stringent regulatory requirements for determining whether the assumed harms are only a "minor" increase over minimal risk, whether the participants have a "condition," and whether the research holds out the prospect of direct benefit to participants and precludes use of the regulatory standard for waiver of guardian permission.

A limited number of examples of "minimal risk" are included in the expedited review categories in the *Code of Federal Regulations*. However, these examples are limited, and none are specific to children, which inadvertently restricts minimal risk approval for pediatric research because IRBs are reluctant to go beyond the specific examples. As a conseqence, several federal advisory boards and research organizations have recommended that the Office of Human Research Protections provide age-indexed examples of minimal risk research to reflect the different daily and medical experiences of infants, children, and adolescents and that OHRP direct IRBs to use the "well child" pediatric visit and the pediatric mental health interview as reasonable benchmarks for determining whether research procedures are equivalent to experiences of minors during routine medical and psychological examinations or tests.[7] These age-graded benchmarks would facilitate IRB approval of research critical to reducing health disparities for LGBT youth since questions involving emotional well-being, substance use, and sexual activity are a routine part of medical and psychological examinations and tests involving adolescents.

Guardian Permission Waivers

Following the Belmont principle of *respect*, informed consent protects participants' autonomy and welfare, enabling individuals to make an informed, rational, and voluntary decision about whether to participate in research. Consent procedures for children require special consideration for several reasons. In many instances, minors do not have the legal status to consent, and for younger children, the level of cognitive and emotional development and lack of experience making independent health care choices may compromise their ability to make an informed and voluntary research participation decision. Guardian permission is thus often seen as the best way to ensure that minors' decisional rights are protected.[8] However, a significant body of research on the ability of youth ages fourteen years and older to understand the nature of and research rights associated with medical and mental health research at levels similar to adults suggests that guardian permission may not be a necessary protection for the rights of adolescents to make an informed research participation choice.[9] For LGBT adolescents, guardian consent may in fact be a barrier to opportunities to participate in research that poses the probability of direct health benefits or indirect benefits to other LGBT youth.

Data indicate that, more than other youth, those who are LGBT may avoid participation in studies that require guardian permission; among reasons for this are that some LGBT youth are not open about their sexual orientation, have not gained support from all or some family members,

have been victimized by their families following disclosure of sexual orientation, or fear that parents will assume participation is an admission of sexual activity.[10] Requiring guardian permission can also jeopardize the involvement of LGBT youth in health research utilizing social media, mobile phones, and other new technologies to better address privacy concerns and recruit members of a hidden population of LGBT youth who see these technologies as an opportunity to gain information about sexual behaviors, STIs, and sexual identities and to receive social support.[11]

Under 45CFR46.408, IRBs are permitted to approve a waiver of guardian permission for minimal risk research if the research could not be "*practicably carried out*" without the waiver or the waiver is "not a reasonable requirement to protect the subjects." Yet many IRBs refuse to waive the guardian permission requirement for adolescent research in general, and LGBT youth research specifically, based on overestimations of research risks and lack of clarity about the meaning of the terms "practicably" and "reasonable." For this and related reasons, the Secretary's Advisory Committee on Human Research Protections recommended that OHRP direct IRBs to consider that studies involving high school students who may not have revealed their LGBT identity to their parents be accepted as studies that meet both the "practicably" and "not reasonable" requirement for guardian permission waiver in that they offer a credible argument that serious physical, social, or psychological harm may come to child subjects if parents or guardians are informed about the reason for the study."[12]

IRBs sometimes also refuse to issue appropriate waivers of guardian permission in order to avoid liability based on perceived barriers created by ambiguous state laws concerning youth access to health research. Under federal regulation 45 CFR 46.402a, minors who "can consent to treatments or research under the applicable law of the jurisdiction in which research is conducted" are considered adults and thus can independently consent to research participation. However, since most state emancipated and mature minor laws do not include language specific to research participation, many IRBs continue to treat LGBT adolescents as "children" and needlessly require guardian permission for their involvement in research related to mental health, substance abuse, and sexual health services for which they have obtained legal adult status. This had led several federal advisory committees and research organizations to recommend that OHRP issue guidance to IRBs to facilitate the appropriate waiver of guardian permission and clarify that persons who by state law are considered "mature" or "emancipated" minors be accorded adult status when asked to consent to participate in research related to health services and procedures for which they are legally entitled to provide autonomous consent.[13]

Reducing Health Disparities and Giving Voice

Mental and sexual health treatment efforts and substance abuse prevention efforts for LGBT adolescents in the United States and around the world are compromised by a lack of rigorous clinical trial evidence to support treatment choices and prevention approaches, thereby requiring physicians to extrapolate from studies in older adult populations. Substantial biomedical and psychosocial data suggest that adolescents are not simply smaller adults and that making such assumptions results in less than optimal care. Brain development continues into early adulthood, particularly in the brain's cognitive control system that improves capacity for self-regulation. This creates a "developmental mismatch" during adolescence in which neural structures involved in processing reward and emotional cues develop, while behavioral and emotional regulation are still relatively immature.[14] Consequently, adolescents may not respond in the same way to interventions developed for adults.

To adequately understand and develop interventions to reduce health disparities affecting LGBT youth requires promotion of ethically responsible research practices based on sound empirical data rather than subjective and unfounded assumptions. Listening to the voices of LGBT youth is an essential means to attain these goals.

The landmark United Nations' Convention on the Rights of the Child established international recognition that children should have a voice in decisions that affect their well-being.[15] However, investigators and IRBs traditionally draw on their own moral compasses in applying federal regulations to plan ethical procedures. The perspectives of participants are given only superficial consideration through the appointment of a community IRB member who cannot realistically represent the perspectives of the diverse individuals who will be called upon to participate in various research projects conducted by members of the institution. Thus the participation of stakeholders in the design and implementation of research and human subjects protections is increasingly seen as a moral imperative for the conduct of responsible research involving socially disadvantaged populations.[16] However, it has yet to be extended to sexual minority youth. Studies that have drawn on the perspectives of youth and their parents on the ethical dimensions of adolescent health research have helped to correct common IRB misperceptions including erroneous assumptions that (a) simply answering survey questions about sexuality, drug use, or suicidality encourages youth to engage in such activities or is more stressful than answering such questions in routine medical examinations; (b) parents find waiver of guardian permission for such studies unacceptable; and (c) parents would refuse to consent to such studies if youth were offered postexperimental

referrals for appropriate services independent of guardian notification.[17]

On account of sexual orientation and gender identity, family and social contexts, and developmental changes in the brain, evaluations of human subjects protections by LGBT youth will invariably differ from those by IRBs and research professionals. The views of LGBT youth are thus critical to identifying human subjects interventions that may or may not present minimal psychological or social harms, jeopardize participant privacy, or threaten or support participant autonomy not readily discerned through professional logic, scientific inference, or the context-free application of federal regulations. Engaging prospective participants in the design of ethically responsible practices will help transform research involving LGBT youth into an evidence-informed process that will protect their rights and welfare and reduce undue barriers to participation in research critical to the future health of this population.

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