Title: Adolescents, Sensitive Topics, and Appropriate Access to Biomedical Prevention Research

Open Peer Commentary on "IRBs and The Protection-Inclusion Dilemma: Finding a Balance"

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Adolescents, Sensitive Topics, and Appropriate Access to Biomedical Prevention Research

Adolescence, defined in the US as 11-21 years of age, is a critical period for prevention, as it marks the onset of risk behaviors. Minor (< 18 years) self-consent and inclusion in biomedical research (drugs, vaccines, procedures) on sensitive topics remains controversial, and minors are frequently excluded from biomedical prevention research. For example, oral HIV pre-exposure prophylaxis (PrEP) can prevent up to 95% of new infections. PrEP was FDA approved in the United States in 2012 for adults, but took another 6 years to be approved for minors.

Appropriate access is inclusion with protection. US regulatory guidance identifies the inclusion of children in medical research as an important goal (U.S. Food and Drug Administration, 2019). Appropriate access occurs when researchers identify characteristics and contexts that render individuals vulnerable and design research procedures to mitigate those vulnerabilities. Age-related disparities in access to research for adolescents stem from a regulatory definition of children that is developmentally inconsistent, a group-based approach to child vulnerability, and a failure for regulations to account for the developmental changes in capacity of adolescence.

Adolescents are not recognized as a distinct regulatory category in the US. Adolescents are either considered children, with corresponding high levels of protections, or adults, with no additional protections. Children are individuals who cannot consent to *clinical care* in the jurisdiction of the study (U.S. Department of Health & Human Services, 2021). While this is 18 years for general medical care, the age is lower and varies state-to-state for research on sensitive topics. For example, a 16 year old in one US state may be able to consent to

contraception, and thus would not be considered a child for contraception research, whereas a minor in a neighboring state without a similar minor consent law may not. This focus on legal, rather than developmental, capacity results in inequitable access to research by geographic location, acts as a barrier to multisite research, and is developmentally inconsistent. With increasing state-level restrictions in adolescent access to reproductive health care, the approach will lead to increased exclusion of adolescents from research.

A second barrier to appropriate access in US regulations is a group-based approach to vulnerability. Persons who fit into specific categories, such as children, prisoners, and pregnant persons, are considered vulnerable, with that vulnerability linked primarily to risk of undue influence or coercion (Friesen, in press). For children, parental permission coupled with child assent forms the core of protection (U.S. Department of Health & Human Services, 2021; U.S. Food and Drug Administration (FDA), 2013). This group-based approach to child vulnerability is problematic for research on sensitive topics for adolescents. With sensitive topics, the primary protection for children, parental permission, can introduce harm through an unintentional disclosure of risk behaviors or minoritized identities. For example, in the US, HIV disproportionately affects gay males and transgender females of color, and there is a need for these adolescents to participate in HIV biomedical prevention studies. But requiring parental permission not only increases the risk of disclosure to parents about the minor's HIV risk behaviors, but also the risk of disclosure of their gender identity and/or sexual orientation. Requirement for parental permission discourages minors from participating in research on sensitive topics, creating an age-related inequity. Among minors who self-consented for a PrEP research trial, none of the interviewed minors consulted a parent/guardian prior to

participating, and a high proportion stated that they would not have participated if parental permission were required (Knopf et al., 2017).

A third barrier to appropriate access is that the binary child/adult categorization in US regulations is missing a recognition of adolescent development. Many of the ways younger children are vulnerable, including decreased capacity to consent, being excessively deferential to adults where they might not feel they can refuse, or legally not able to consent for themselves, are frequently not true for adolescents.

A more robust regulatory definition of child and adolescent vulnerability needs to incorporate adolescent development. Global regulatory guidance (The Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization, 2016) define vulnerability in research as an increased likelihood of experiencing harm. A developmental approach recognizes that the type, severity, and likelihood of harm for children will vary across childhood. By taking into account the developmental characteristics of the age group (e.g. cognitive ability, legal standing, independence from parents, behavioral experience) and contexts (stigma and sensitivity of the topic, family structure, poverty, belonging to a minoritized racial group), a developmental approach can potentially provide additional protections and lead to appropriate access. Specific domains in which children and adolescents are vulnerable has been described (see, for example, (The Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization, 2016)), and can form the foundation for a list of considerations for an IRB.

For adolescents, capacity to consent is the most frequent vulnerability brought up in ethics review. However, advances in decision-making research and adolescent brain science

allow a better understanding of adolescents' capacity to consent and need for adult support. Despite common perceptions of adolescents as poor decision-makers, by ages 12-14, adolescents have been shown to have research decision-making capacity in both actual and simulated clinical trials similar to adults. Capacity to consent includes understanding study information, appreciating how it would affect them, reasoning about risks and benefits, and making a voluntary choice (Appelbaum & Grisso, 2001). Adapting the Macarthur Competence Assessment Tool for Clinical Research (MacCAT-CR) for children, Hein et. al. found that by 12 years of age, children enrolling in pediatric research in a Children's Hospital demonstrated adequate capacity (Hein et al., 2015). In work by our group and Kreniske, using an adaptations of the MacCAT-CR, all middle adolescents (15-17 years old) and most early adolescents (12-14 years old) demonstrated capacity to consent to a simulated biomedical clinical trial research (Ott & McGregor, 2016) or to actual HIV research (Kreniske et al., 2022).

Waivers of parental permission are an aspect of ethics review that could be improved with a more developmentally informed definition of vulnerability. There is longstanding agreement to waive parental permission in lower risk research when it introduces physical, emotional, or social harm; however, it is less clear whether adolescent self-consent or a surrogate consent might be substituted. In sensitive topics research, IRBs frequently allow adolescents to self-consent for research when they can legally consent to related care in their jurisdiction. As noted above, however, this leads to geographic inconsistencies, particularly with the state laws limiting minor consent for clinical care. For example, despite wide agreement that adolescent self-consent and confidentiality for contraceptive care is a best clinical practice, only 34 US states have laws allowing minors to consent to contraception. Linking research

consent to clinical care consent make sense from a justice perspective, in that adolescents participating in research should not experience additional harms through loss of confidentiality and disclosure compared to adolescents receiving clinical care. However, this fairness would only be achieved when the standards for adolescent clinical care are based upon a developmentally informed standard, rather than the current state-by-state variation. One solution for an appropriate developmental standard would be using international clinical guidance that employ an explicit developmental framework. For example, rights to confidential care for reproductive health are clearly identified in the World Health Organization's Global Standards for Quality Healthcare Services for Adolescents (World Health Organization & UNAIDS, 2015).

The US approach to vulnerability only identifies limited types of protections or safeguards for biomedical research, and these focus primarily on the consent process (Friesen, in press). However, there are a broader array of potential protections to support adolescents in ways they are vulnerable. CIOMS identifies safeguards such as interventions to promote voluntary decision-making, limit confidentiality breaches, and changing research procedures to minimize harms. Alternative consent processes, such as allowing adolescents to decide whether to involve a parent, supportive decision-making, and community consultation may also provide protections that can be more developmentally tailored.

A developmental lens will need to be applied to the process of protocol review. Reviewer should have relevant developmental expertise. For protocols with adolescents on sensitive topics, this would include some experience in sensitive topic areas generally and adolescents specifically. An appropriate community representative, someone from those

communities most affected by the sensitive issue, could provide insight into the values and preferences of those most invested in the health and safety of the adolescent participants.

In sum, a new regulatory definition of child and adolescent vulnerability would start with a recognition of adolescence as a distinct developmental stage relevant to research, and defining vulnerability as characteristics and contextual factors that put the adolescent at increased risk of harm from the research. Ethics committees would need to consider how the research design can support participants in ways they vulnerable and to mitigate harms.

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