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Commentary

World Health Organization Guidance on Ethical Considerations in Planning and Reviewing Research Studies on Sexual and Reproductive Health in Adolescents

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Adolescence—defined by the World Health Organization (WHO) as the second decade of life (10–19 years of age)—is a time when significant physical, psychological, and social changes occur. During this period of development, adolescents gain more advanced patterns of thinking and reasoning, seek to forge their own identities, form new social relationships and attachments, and develop an increasing sense of responsibility and independence. It is also a time when adolescents may face social challenges such as inadequate educational opportunities, limited prospects for finding rewarding work, and health challenges such as early and unintended pregnancy, sexually transmitted infections, violence, anxiety, and depression [1,2].

Adolescents constitute approximately 1.2 billion of the world's population. The physical and social world in which they are growing up is changing, with growing urbanization, changing social norms, and shifting trends in age of marriage and premarital sexual activity. Now more than ever, focused research on the sexual and reproductive health of adolescents is urgently needed to fill gaps in data and inform successful programs and policies to meet the needs and fulfill the rights of adolescents. However, such research presents complex ethical and legal challenges. By late adolescence, many individuals first become sexually active. Sexually active adolescents, including those in early or forced marriage, may face significant barriers in accessing the information, support, and services they need to make safe and informed decisions regarding their reproductive lives [2,3]. Such barriers to support adolescent sexual and reproductive health may have far-reaching implications [4]. An estimated 21 million girls aged 15–19 years and 2 million girls aged under 15 years become pregnant in low- and middle-income countries [5,6]. Globally, an adolescent between the ages of 15 and 19 years becomes infected with HIV every 2 minutes, whereas more than 2 million adolescents are living with HIV [7].

In response, the WHO has launched *Guidance on ethical considerations in planning and reviewing research studies on sexual and reproductive health in adolescents* [8] (hereinafter *Guidance*), which provides practical guidance on the most pressing ethical challenges that arise within adolescent sexual and reproductive health research. The *Guidance* may also be instructive for any research involving adolescents.

Why Is New Guidance Needed?

Adolescents aged under 18 years are classified as children in many settings. In terms of the Convention on the Rights of the Child (CRC), a child means "every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier" [9]. In the research context, children are governed differently from adults because of their vulnerability. For instance, children generally lack capacity to participate in research autonomously. Furthermore, mandatory disclosure obligations may apply to children in the research context that do not apply to adults. These factors are especially relevant in research focused on the sexual and reproductive health of children and adolescents. Leading global research ethics guidance documents often serve as models or templates for local guidance documents. In the absence of local governance documents, regulators and researchers often rely on global guidance documents to guide local research activities. Accordingly, the guidance offered by the world's two leading research ethics guidance documents—the Declaration of Helsinki (hereinafter DOH), published by the World Medical Association, and the

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International Ethical Guidelines for Biomedical Research Involving Human Subjects, published by the Council for International Organizations of Medical Sciences (hereinafter CIOMS Guidelines)—are most often relied upon to guide research on adolescents [10,11]. Yet, despite the distinct vulnerability of children and adolescents, and despite the CRC holding that "in all actions concerning children…the best interests of the child shall be a primary consideration" [12], the DOH and the CIOMS Guidelines offer relatively little dedicated guidance on research involving these groups.

Although the DOH provides general ethics guidance that may apply to research on children and adolescents, it offers no guidance specific to children and adolescents. The CIOMS Guidelines dedicates a single provision, Guideline 17, to research on children and adolescents. However, even this provision fails to cover critical issues such as appropriate terminology usage in respect of characterizing adolescents, how to determine the best interest of a child, and how to manage conflicts between law and ethics in the research context. Similarly, other international research ethics guidance documents offer limited guidance on researching children and adolescents. For example, the WHO's *Standards and Operational Guidance for Ethics Review of Health-related Research with Human Participants* [13] offers no dedicated guidance on researching children and adolescents. United Nations International Children's Emergency Fund's series of *Innocenti Briefs* on researching adolescents in low- and middle-income countries [14] offers no guidance on how to manage confidentiality dilemmas in the research context nor how to manage conflicts between ethics and law.

Gaps in global research ethics guidance, coupled with the absence of local ethics guidance specific to children and adolescents in many settings, have contributed to a climate of uncertainty among researchers, sponsors, and regulators. This has led to the exclusion of adolescents in crucial research, which is counter to the best interest of this group [15]. For example, a South African HIV study aimed at collecting data on viral set point, HIV transmission, and disease progression in adolescents aged 14–18 years of age—which is crucial to developing an HIV vaccine—had to be amended to include participants only above the age of 18 years because of perceived ethical barriers [16].

Provenance of the *Guidance*

The *Guidance* is the culmination of a global consultative process. To identify the issues to address, we elicited the opinions of a culturally and geographically diverse panel of 34 experts from various stakeholder groups. We posed the following open-ended question: "What would be some of the key elements that the guidance should capture?" The responses to this question pointed to a short list of priority areas. These were addressed in the initial draft of the document, and subsequent iterations were sent to individuals for review and feedback.

The Scope of the *Guidance*

The consultative process highlighted a need for guidance on four thematic areas, which are explored in dedicated sections in the *Guidance*. Each section is anchored by paradigmatic case scenarios that highlight ethical and legal challenges that typically arise in that thematic area.

Section 1 of the *Guidance* highlights the significance of accurately and uniformly characterizing a proposed study population. The *Guidance* stresses that researchers must use appropriate and consistent terminology for the study population; therefore, there is no ambiguity regarding who is included, and why. Furthermore, it notes that precision in defining the study population can inform clear policy implications and facilitate comparison with other relevant studies. To underscore this point, the *Guidance* surveys a sample of terms that are typically used to describe or characterize adolescents, but which are often distinct and carry different connotations. This includes the terms "adolescent," "child," "orphan," "minor" (including "emancipated minor" and "mature minor"), "juvenile," "paediatric population," "teenager," "young adult," "young person," "youth," and "ward." The *Guidance* notes that there are also definitional inconsistencies implicit in these terms within and between countries, within and between regions, and even at the international level because different social and cultural assumptions underpin many of them.

Section 2 of the *Guidance* explores the notions of autonomy, informed consent, and assent. In exploring the notion of autonomy, the *Guidance* highlights the stance of the CRC on the child and decision-making. It notes that there are both legal and ethical requirements for consent and explores how to determine an adolescent's capacity and maturity in the research context. The *Guidance* suggests factors to consider in assessing a child's capacity to assent and stresses that the notion of "maturity" has both developmental and sociocultural dimensions. It also highlights that there are some differences among professional disciplines on the notion of maturity. Finally, the *Guidance* also explores waiver of parental informed consent and waiver of documentation of informed consent.

Section 3 explores how conflicting ethical and legal obligations with regard to adolescent research participants ought to be reconciled. In doing so, the *Guidance* outlines the CRC's definition of the "best interests of the child" and suggests factors that may be taken into consideration in determining a child's best interests. It notes that the best interests of a child broadly describe the well-being of a child. Furthermore, that well-being is determined by a variety of individual circumstances, including the child's age, level of maturity, the presence or absence of parents, and the child's environment and experiences. This section also considers how to manage studies that focus on a lifestyle or behavior that is considered immoral and classified as unlawful in the local context, such as research on lesbian, gay, bisexual, and transgender adolescents.

Section 4 explores information sharing in the context of adolescents. More specifically, how confidentiality, privacy, disclosure obligations, access to information, and the adolescent's right to be informed of their health status ought to be managed in the research context. The *Guidance* stresses that children have the right to share information, to be informed about pertinent issues related to themselves, and to privacy. However, these rights must be balanced against relevant disclosure obligations, judicial directives, and what is in the child's best interests. The *Guidance* advises research organizations to devise policies or standard operating procedures to govern information sharing in respect of their study participants.

Discussion

The new *Guidance* examines the challenges of applying ethical principles in research with adolescents and proposes practical ways to think through and address those challenges based on a sound understanding of the sociocultural context and the regulatory environment. In doing so, it complements and goes beyond existing research ethics guidance documents.

We hope that the *Guidance* helps researchers, research ethics committee members, program planners, and sponsors to better address the intersection between ethics, law, and social norms and thereby facilitate research with adolescents while ensuring their protection. Such an approach will help us better understand and address the specific needs of this vulnerable population.

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