Guidance on ethical considerations in planning and reviewing research studies on sexual and reproductive health in adolescents
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Acknowledgements

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A technical consultation hosted by the World Health Organization (WHO) Department of Reproductive Health and Research on the sexual and reproductive health of young adolescents in low- and middle-income countries identified a pressing need for guidance on the ethical and safety issues to consider when conducting research with adolescents.

As follow-up to this meeting, a mapping of the available documents related to ethical considerations for sexual and reproductive health research with adolescents was conducted. Next, researchers and programme planners from high-, middle- and low-income countries were identified to define the key content to be included in the guidance document. Deepa Leah Persad solicited and collated feedback from this group, which included Rajib Acharya, Akin Bankole, Carmen Barroso, Linda-Gail Bekker, Marissa Billowitz, Claire Brindis, Fabian Cataldo, Marinella Della Negra, Jessica Dietrich, Annabel Erulkar, Adesgun Fatusi, Sarah Flicker, Janet Frohlich, Loretta Gavin, Marianne Haslegrave, Shireen Jejeebhoy, Rachel Jones, Susan Kasedde, Sabrina Kitaka, Sonal Mehta, AJ Melnikas, Ramiro Molina Cartes, Busiswe Nkala, Friday Okonofua, Helen Rees, Michael Resnick, John Santelli, Katie Schenk, Vinit Sharma, Renee Sieving, Susheela Singh, Catherine Slack, Ann Strode, Cynthia Summers, Johanne Sundby and Melissa Wallace. Based on the input received, a concept note was prepared.

In consultation with the WHO Ethics Review Committee, Jerome Amir Singh (Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa, and Dalla Lana School of Public Health, University of Toronto, Toronto, Canada) was engaged to draft the document. The first draft was reviewed by a subgroup of the stakeholders consulted earlier, including Akin Bankole, Marinella Della Negra, Lee Fairlie, Lawrence Finer, Loretta Gavin, Shireen Jejeebhoy, Rachel Jones, Sabrina Kitaka, AJ Melnikas, Busiswe Nkala, John Santelli, Vinit Sharma, Susheela Singh, Catherine Slack, Ann Strode, Cynthia Summers and Melissa Wallace. Abha Saxena, Secretary of the WHO Ethics Review Committee, also reviewed the document and obtained inputs from researchers within and outside WHO.

The second draft received comments from researchers involved in the Global Early Adolescent Study, including Omaima El-Gibaly, Eleanor Faur, Caroline Kabiru, Chaohua Lou and Kristien Miichielsen, who provided valuable inputs informed by their experiences in the field.

Drawing upon the feedback of these groups, a revised third version of the document was developed. Following a field test in South Africa by Jane Ferguson, the guidance was strengthened further. Pooja Parameshwar and Manahil Siddiqi, two young researchers, reviewed the document and provided input and feedback on the third draft.

Venkatraman Chandra-Mouli from the WHO Department of Reproductive Health and Research led the development of the document.
<table>
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<th>Abbreviation</th>
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<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
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<td>CRC</td>
<td>Convention on the Rights of the Child</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>ICH</td>
<td>International Council for Harmonisation</td>
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<td>UNFPA</td>
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Introduction

Adolescence – defined by the World Health Organization (WHO) as the second decade of life – is a time when enormous physical, psychological, and social changes occur. This is a time when individuals initiate and experiment with “adult behaviours”, such as sexual activity and substance use (1). These behaviours can result in negative health outcomes, such as unintended pregnancy and sexually transmitted infections, and negative social outcomes, such as school dropout and social exclusion (2, 3).

Research relating to this population is crucial. However, the participation of adolescents in health research poses legal and ethical challenges, particularly when the research focuses on sexual and reproductive health. This document highlights some of these challenges and outlines how they may be addressed. It is intended to provide practical guidance to people involved in sexual and reproductive health research with adolescents.

Background

In order to identify the issues this document should 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 were incorporated into the initial draft of the document, and subsequent iterations were sent to individuals for review and feedback. Of those consulted: 50% were from low- and middle-income countries (LMICs) and 50% from high-income countries; 67% were female and 33% male; and 41% were from academia, 35% from international nongovernmental organizations, 21% from United Nations agencies, and 3% from governmental bodies. This document is based on the four broad themes that emerged from this consultative process.

Structure and scope

Section 1 highlights the significance of accurately and uniformly describing a proposed study population. In doing so, it surveys a sample of terms that are used to typically describe or characterize adolescents. Section 2 explores the notions of autonomy, informed consent and assent, and how to determine an adolescent’s capacity and maturity in the research context. Section 3 explores the nature and implications of the principle “best interests of the child”, and how this notion should be applied when researchers encounter a conflict between their ethical and legal obligations in relation to adolescent research participants. Section 4 explores information-sharing in relation to adolescents in the research context.

The limitation of the scope of this document to these four themes does not mean that other themes and issues – which apply to study participants of all ages – are unimportant. Ethical research for all...
age groups, including adolescents, must uphold the principles of respect for people, beneficence and justice. These principles are clearly described in recently updated guidelines by WHO and the Council for International Organizations of Medical Sciences (CIOMS) (4). Special considerations in addressing adolescents are discussed in key complementary documents included in the references. Given that the document focuses on the four themes identified through the stakeholder consultative process, it cannot be regarded as exhaustive regarding the ethical considerations of research with adolescents.

This document is intended to address commonly occurring situations and challenges that are faced in carrying out research with adolescents (people aged 10–19 years), the majority of whom are deemed not to have reached the recognized age of majority in their respective settings. To this end, adolescents aged 18 and 19 years are classified as adults in many settings and have the legal capacity to make autonomous decisions regarding their participation in research. In this document, the term “children” refers to people below the age of 18 years, and the term “minor adolescents” refers specifically to people aged 10–18 years.

While some of the guidance in this document may not be applicable to all settings and instances, it is hoped that it serves as a starting point for discussion and reflection on how a particular issue may be managed in a certain context or setting. The document is intended to complement and supplement existing norms and guidance documents, rather than to replace them.

**Who should use this guidance**

This document is designed to inform people involved in sexual and reproductive health research with adolescents. This includes (but is not limited to) researchers, research ethics committee members, programme planners and sponsors.
1 Defining the study population

1.1 Introduction

The appropriate use of terminology in a study protocol is crucial, particularly as doing so impacts study design, including inclusion and exclusion criteria. When a definition is not clear and consistent, difficulties arise in applying the study’s findings and in comparing them with findings from other studies. This section focuses on the major technical definitions that pertain to various groups of adolescents, and also discusses the implications of conducting research with these different groups. In so doing, this section briefly touches on the concepts of autonomy, informed consent and assent. Each of these concepts is explained in greater detail in Section 2.

Case scenario 1

A researcher intends to conduct a study to determine the prevalence of sexually transmitted infections among adolescents in a rural area of a Latin American country. The study protocol makes varying references to “youth”, “young people”, “teenagers” and “mature minors” in relation to the proposed study respondents. The protocol’s stipulated inclusion age criterion is 10–19 years. What impact could the researcher’s use of these different terms have on the study’s proposed design, particularly its inclusion criteria, and its generalizability?

1.2 Pertinent information necessary to resolve Case scenario 1

A range of terminology applies to adolescents. 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”.

Although these terms may appear similar, and even occasionally overlap in meaning, they have particular legal, social, cultural and health connotations and implications. 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 the definition of “youth”. These assumptions are often based loosely on the onset of menarche for girls and puberty for boys, or on particular coming-of-age rituals or rites of passage linked to manhood or womanhood, marriage, parenthood or employment (5,6).

The terms described below are used widely in the literature to denote adolescents.
1.2.1 Adolescents

Adolescence has been described as “a cultural construct that varies across settings and contexts” (7). In the United Nations system, adolescence is generally ascribed to the stage of life between puberty and adulthood (8). United Nations entities, such as the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), the United Nations Population Fund (UNFPA) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), define an adolescent as an individual in their second decade of life (aged 10–19 years), with a “young adolescent” being defined as a person aged 10–14 years and an “older adolescent” as a person aged 15–19 years (9). It is important to note that different age ranges are used by other organizations in relation to adolescents. For example, the International Council for Harmonisation (ICH) defines adolescents as individuals aged 12–16 or 12–18 years of age, depending on region (10). The definition may also differ by country. In Bangladesh, for example, adolescents have been defined variously, including 9–19 years of age (11) and 15–24 years of age (12). However, chronological age is just one way of defining adolescence. Adolescence can also be defined in numerous other ways, including in terms of physical, social, moral, emotional and cognitive development (13,14).

The implication for research is that adolescents include those treated as children or minors in their national jurisdiction, and thus do not have the legal right to consent to research autonomously, as well as those who are deemed adults from a legal perspective because they are over the age of 18 years, and thus have the legal right to consent to research autonomously.1

However, the term “autonomy” has important nuances to be considered. Many autonomous individuals (people who can legally consent independently to participation in research) have historically been unable to exercise their autonomy: they have been deprived of the right to make their own decisions due to discrimination. In addition, even after some adolescents have reached the legal age to provide autonomous consent for research participation, they may still defer to parents or family members in decision-making.2 Although minor adolescents are not recognized as having autonomy to provide legally valid consent for their participation in research, their emerging decision-making capacity and autonomy should be taken into account through processes such as informed assent (see Section 2.2.2 Autonomy) (13).

1.2.2 Children

The United Nations Convention on the Rights of the Child (CRC) defines a child as a “human being below the age of 18 years” (16). The end of adolescence and the beginning of adulthood (the age when a child is no longer regarded as a minor) varies by country and context. For example, in South Africa, a child is legally defined as an individual under the age of 18 years (17), while the country’s HIV management guidelines define a child as a person who is “10 years of age and younger” (18). For the purposes of the clinical investigation of medicinal products in paediatric populations, ICH classifies a child as being 2–11 years of age (10). In settings that legally classify adults as individuals above the age of 18 years regardless of other considerations, 18- and 19-year-olds are legally adults but still adolescents under the United Nations definition of adolescence.

1 In this document, we use the term “autonomy” as defined in the Belmont Report (15). Respecting autonomy requires the recognition of autonomous individuals – that is, people who are capable of self-determination, to make informed choices about their own participation in research without coercion or obstruction.

2 In this document, the term “parent” is used for simplicity, but it includes legal guardians.
The implication for research is that adolescents who are classified as children do not have the right to participate in research autonomously, unless the requirement of soliciting parental consent has been waived by relevant authorities (see Section 2.2.6 Waiver of parental informed consent). Some settings require that even if a child’s parent or guardian provides consent to participation in research, the child must also assent to it.

Children who lack adult guardianship in the context of research, or adults who can legally provide consent for the child’s participation in research, need to be treated with particular care. The consent processes to be used when engaging these children in research are discussed below.

1.2.3 Children living in difficult circumstances

1.2.3.1 Children “left behind”

According to UNICEF, despite significant progress and achievements in human development, unequal opportunities have resulted in millions of people dying before they turn five years of age, suffering chronic malnutrition, living in poverty, and going without schooling. In this context, children who have failed, or are failing, to enjoy the benefits of human progress – including in relation to material well-being, educational achievement and health – have been described as children who have been, or are being, “left behind” (19). This designation is distinct from the description “left-behind children” (see below). A child “left behind” does not necessarily lack a parent or guardian to provide informed consent for their participation in research. As children “left behind” may well have parents or guardians, the implication for research is to seek informed consent from their parent or guardian, following standard informed consent processes.

1.2.3.2 Left-behind children

The International Labour Organization (ILO) defines left-behind children as children who are left behind in their country of origin by one or both parents who are migrating elsewhere for employment opportunities. Children who are left behind by a parent may live with one of their parents, relatives or non-related caregivers or even alone with siblings (20,21). In some instances the description of a left-behind child may seem to overlap with the description of a “social orphan” (see Section 1.2.3.4 Orphans). While there is no consensus regarding how long a child needs to be left behind in order to qualify for such a status, some studies have prescribed a minimum period of at least six months (22). The relevance of such a definition for research purposes is that in the case where only one parent has left the child behind and the other parent is living with the child, a researcher would have to seek informed consent from the parent taking care of the child, for that child’s participation in research. In the case where both parents have left the child behind, a researcher would have to determine whether there is any responsible adult or appointed guardian overseeing the child’s welfare, and whether that individual is authorized in terms of local laws to provide informed consent in lieu of the parent(s) for that child’s participation in research.

1.2.3.3 Children in child-headed households

UNICEF has defined a child-headed household as a household “where no adults – parents or guardians – can be identified, and the child is responsible for the care of other, younger children” (23). While some countries, such as Namibia, define such households as “meaning a household headed by a child under the age of 18” (24), other countries, such as South Africa, describe such households as one where “a child over the age of 16 years has assumed the role of caregiver in respect of the
children in the household” (25). The implication for research involving children in such households is that informed consent for such children may need to be solicited from a court or relevant health or social welfare authorities (where permissible). Alternatively, researchers may wish to explore whether the governing research ethics committee overseeing the proposed study is authorized to waive parental consent.

1.2.3.4 Orphans

UNICEF and other agencies define an orphan as a child who has lost one or both parents (26). This definition contrasts with the definition used in some countries, where a child must have lost both parents to qualify as an orphan. According to UNICEF, UNAIDS and the United States Agency for International Development (USAID), orphans may be divided into several subcategories:

- Double orphan: a child aged under 18 years whose mother and father have died.
- Maternal orphan: a child aged under 18 years whose mother (and perhaps father) has died (includes double orphans).
- Paternal orphan: a child aged under 18 years whose father (and perhaps mother) has died (includes double orphans).
- New orphan: a child aged under 18 years who has lost one or both parents in the past year.

In addition to the above terms, the term “social orphan” has been used to describe children “whose parents may be alive but who are neglected or abandoned by their parents or whose parents are no longer fulfilling any of their parental duties” (27). In some instances, this definition may seem to overlap with the description of left-behind children (see Section 1.2.3.2 Left-behind children).

The implications for research in relation to orphans is that a double orphan may be deemed a ward of the state. In such instances, a designated official would have to provide informed consent for the child’s participation in research. The same may be true for social orphans who are not under the care of a designated caregiver. If an orphan child has been placed in foster care, the foster parent may be authorized to consent to the child’s participation in research. In the case of an orphan who has lost one parent and who is being cared for by the other parent or a designated guardian, then that responsible adult will usually be able to consent to the child’s participation in research.

1.2.3.5 Street children

UNICEF has defined and placed street children in three categories (28):

- Street-living child: a child who has run away from his or her family and lives alone on the streets.
- Street-working child: a child who spends most of their time on the streets, fending for themselves, but returning home on a regular basis.
- Child from a street family: a child who lives on the streets with his or her family.

These distinctions are important for research since street-working children and children from street families have families and homes to go to (and so informed consent for the child’s participation in research may be solicited from a traceable parent or guardian or, in some cases, where permissible, an authorized responsible adult or caregiver), whereas a street-living child has no responsible adult overseeing his or her welfare. In such instances, a government authority or court may need to be approached to provide informed consent for that child’s participation in research.
1.2.3.6 Unaccompanied children seeking asylum

The Office of the United Nations High Commissioner for Refugees (UNHCR) defines an unaccompanied child seeking asylum as “a person who is under the age of 18, unless, under the law applicable to the child, majority is attained earlier and who is separated from both parents and is not being cared for by an adult who by law or custom has responsibility to do so” (29). UNHCR recommends that a guardian or adviser be appointed as soon as the unaccompanied child is identified. In this respect, the guardian or adviser should have the necessary expertise in the field of childcare to ensure the interests of the child are safeguarded and the child’s needs are appropriately met, and the child’s legal, social, medical and psychological needs are covered appropriately during the refugee status determination procedures and until a durable solution for the child has been identified and implemented (29). To this end, the guardian or adviser would act as a link between the child and existing specialist agencies and individuals who would provide the range of services required by the child. The implication for research in relation to this category of children is that authority to provide consent for the child to participate in research may vest with the appointed guardian, a government department or a court, until the child is placed in the care of a designated responsible adult or caregiver.

1.2.3.7 Unaccompanied alien (undocumented, illegal immigrant) children

An undocumented immigrant child who is not in the custody of his or her parent(s) or guardian is referred to as an “unaccompanied alien child” in some jurisdictions, such as the United States of America. In such settings, an unaccompanied alien child may be defined as a person who is under the age of 18 years; who lacks lawful immigration status; and who either has no parent or legal guardian (in the country concerned) or has no parent or legal guardian (in the country concerned) who is available to provide care and physical custody of the child (30). The implication for research is that authority to provide consent for the child to participate in research may rest with a government department or a court, until the child is placed in the care of a designated responsible adult or caregiver.

1.2.4 Minors

The legal definition of the term “minor” varies between settings. In some countries, such as India (31), a minor is an individual under the age of 18 years, while in other countries, such as Swaziland (32), the term applies to people under the age of 21 years. In some contexts, a person’s status as a minor can change through marriage. Furthermore, in some settings, minors may be granted legal autonomy at different ages for various activities, including consent for sex, voting, purchase of alcohol and cigarettes, obtaining contraception, and obtaining a driving licence. Once an individual legally attains the status of an adult, he or she is automatically emancipated from parental custody and control.

In some settings, minors may be treated as adults in certain contexts, as explained below.

1.2.4.1 Emancipated minors

Generally, an emancipated minor is a child who has been granted the status of adulthood by a court order, law or other formal arrangement (33). In practical terms, this means that the emancipated minor is freed from parental custody and control, and empowered to make autonomous decisions in particular contexts. Emancipation may occur in several ways, including judicially (through a court order following the minor’s petition of the court), through circumstance (e.g. abandonment or death
of the child’s parent or guardian), through marriage, through joining the armed forces, or expressly (e.g. in Louisiana in the United States, a parent or guardian may emancipate a child under their guardianship by formal declaration before a notary public in the presence of two witnesses) (34). In most settings, a pregnant minor who is unmarried or widowed is still subject to parental or guardian control, and parental or guardian consent will usually need to be solicited for the minor’s participation in research. In some settings, a female minor may be deemed to be socially or legally emancipated if she is married, is pregnant or has a child, and may be afforded exclusive decision-making authority in respect to her own health and that of her offspring, in both the therapeutic and research context.

In other settings, a minor and his or her offspring may be subject to the legal authority of the minor’s parent(s) or guardian. In the latter instances, the research consequence is that informed consent will need to be solicited from the parent or guardian of the minor for any research involving the minor or the minor’s offspring.

Some countries lack formal regulatory frameworks to legally emancipate minors. Even in countries that permit this, the minor’s autonomy may have constraints. For example, an emancipated minor may still be prohibited by law from engaging in certain activities, such as driving or voting.

### 1.2.4.2 Mature minors

The “mature minor” doctrine is a statutory, regulatory or policy concept that recognizes that a minor is allowed to consent or refuse to consent to his or her medical treatment if it is established that the minor is sufficiently mature to understand, discern and appreciate the benefits and risks of the proposed medical treatment (35).

Many countries do not recognize such a notion – and even if they do, they do not recognize it in all contexts. In the United States, for example, courts have ruled that seven factors should be weighed in declaring a minor a mature minor: age, ability, experience, education, exhibited judgement, conduct, and appreciation of relevant risks and consequences (36).

Moving to a different but related issue, some countries have ruled that if a procedure involves minimal risk, minors can consent to them on their own. For example, the United States National Commission for the Protection of Human Subjects of Research has recognized that parental permission for a child’s participation in research is not reasonable where the child is a mature minor and the procedures involved entail no more than minimal risk that such individuals might reasonably assume on their own (37).

When planning research that could involve decisions regarding mature minors, researchers will need to find out what rules and procedures are in place in the setting.

### 1.2.5 Juveniles

The United Nations defines a juvenile as “a child or young person who, under the respective legal systems, may be dealt with for an offence in a manner which is different from an adult” (38). In settings such as the United States, the term refers to an individual who has not attained their 18th birthday, while juvenile delinquency is a violation of law committed by a person before their 18th birthday that would have been a crime if committed by an adult (39). In such settings, a person aged over 18 years but under 21 years is accorded juvenile treatment if the unlawful act occurred before their 18th birthday (39). Such a distinction could be important in the context of research among adolescents.
in detention centres. In this context, restricting the sample population to juvenile adolescents could result in exclusion from studies of adolescents who committed crimes before 18 years of age but are being detained because they have not attained the age of 21 years.

When conducting research with juvenile populations, whether they can participate autonomously in research will depend on relevant domestic laws and policies. In settings where juveniles have the right to participate autonomously in research, such participation may still be subject to authorization by penal authorities (40,41).

1.2.6 Paediatric population
The European Parliament and the Council of the European Union define the term “paediatric population” as “that part of the population aged between birth and 18 years”. While recognizing there is “considerable overlap in physical, cognitive, and psychosocial development across the age categories”, ICH (10) and the European Medicines Agency (EMA) (42) further classify the paediatric population in completed days, months or years, as follows:

- preterm newborn infants
- term newborn infants (0–27 days)
- infants and toddlers (28 days to 23 months)
- children (2–11 years)
- adolescents (12–16 or 12–18 years, depending on region).

The research implication is that in many settings, paediatric populations do not usually have the right to participate in research autonomously unless there are any special conditions for exemption.

1.2.7 Teenagers
The term “teenager” is used widely in the lay literature to denote individuals aged 13–19 years. Some United Nations bodies use the same definition in their documents (43,44).

With regard to research implications, in most settings, teenagers who are 18 or 19 years of age have the right to participate in research autonomously.

1.2.8 Young adults
Adolescents include individuals aged 18–19 years. However, while such individuals are regarded legally as adults in many jurisdictions, they are not classified as young adults by the United Nations. Because of the physical, psychological and sociological differences over the ages of 10–24 years, the United Nations distinguishes between younger adolescents (aged 10–14 years), older adolescents (aged 15–19 years) and young adults (aged 20–24 years) (44). Some developmental psychologists define young or prime adults as individuals aged 20–40 years (45,46). Similarly, while many scientific studies are consistent about when young adulthood begins, there is a lot of variation in the upper cut-off age, ranging from 24 to 29 to 39 years (47).

The implication for research is that individuals aged 18 and 19 years should not be described as “young adults” in research protocols as the United Nations regards this term as applying to adults aged 20–24 years. Instead, cohorts aged 18 and 19 years should be described as “older adolescents.”
1.2.9 Young people

All United Nations entities, including UNHCR (48) and UNFPA (49), define young people as being 10–24 years of age. The African Youth Charter defines young people as “every person between the ages of 15 and 35 years” (50). The implication for research is that young people over the age of 18 years generally have the right to participate in research autonomously.

1.2.10 Youth

Statistical definitions of the term “youth” vary considerably. For statistical consistency across regions, the United Nations defines youth as people between the ages of 15 and 24 years, without prejudice to other definitions by Member States (51). All United Nations statistics on youth (including United Nations agencies such as ILO and UNICEF) are based on this definition. According to the United Nations Educational, Scientific and Cultural Organization (UNESCO), however, the term “youth” is best understood as “a period of transition from the dependence of childhood to adulthood’s independence and awareness of our interdependence as members of a community” (52). Therefore, a youth is often described as “a person between the age where he/she may leave compulsory education, and the age at which he/she finds his/her first employment” (52). This latter age limit has been increasing in recent times, as rising levels of youth unemployment and the cost of setting up an independent household place many young people into a prolonged period of parental dependency.

When applying its Youth Strategy, UNESCO uses different definitions of youth, depending on the context (52). For activities at the national level, UNESCO adopts the definition of “youth” as used by a particular Member State, which may, in turn, be based on regional definitions. In Africa, for example, some countries base their national definition of “youth” on the definition given in the African Youth Charter, where “youth” and “young person” are defined as “every person between the ages of 15 and 35 years” (50); other African countries that are members of the Commonwealth use the Commonwealth definition of 15–29 years (53,54).

In some African countries, such as Ghana, Kenya and the United Republic of Tanzania, the definition of youth used for policy purposes is people aged 15–35 years, while in Nigeria, a youth is defined as a person aged 12–30 years (55). South Africa's National Youth Policy defines a youth as any person between the ages of 14 and 35 years (56).

In Asia, the definition of youth also differs markedly. Nepal, for example, defines youth as people aged 16–40 years (57), while India defines youth as people aged 13–35 years (58).

The implication for research is that people aged 10–19 years should not be described as “youth” in research protocols.

1.2.11 Wards

A ward is generally defined as a child who is placed in the legal custody of the state (59) or court. In the United Kingdom of Great Britain and Northern Ireland, for example, as long as the minor remains a ward of court, all decisions regarding the minor’s upbringing, including medical treatment, must be approved by the court (60). In such instances the ward is placed under the care of a court-appointed guardian or public welfare agency. In settings such as the United States, wards are regarded as vulnerable individuals and are afforded enhanced protection (59).
The research implication is that wards do not have the right to participate in research autonomously. Research participation is thus contingent upon the decision of a legal authority.

1.3 Case scenario 1 resolution

The researcher discussed the terms used in the research protocol with colleagues and familiarized herself with the differences in their meanings. Following discussion and reflection, she decided to remove any reference to the terms “youth”, “young people”, “teenagers” and “mature minors” in relation to the proposed study cohort, realizing that these terms have distinct meanings. Instead, she decided to exclusively use the term “adolescents” to describe the intended study population throughout the protocol, as defined by the United Nations, as this definition best characterized the study’s proposed inclusion criteria. She also chose to further define the sample population for the study by using the age band of 10–19 years.

1.4 Conclusions

People involved in research with adolescents need to be cognisant of the different terms that are used and their precise meanings. Researchers must use appropriate and consistent terminology for the study population so there is no ambiguity regarding who is included, and why. Precision in defining the study population can inform clear policy implications and facilitate comparison with other studies.

Researchers should also make the effort to learn about the different and overlapping terms used within local regulatory contexts. The extent to which there is legal autonomy by age in the local context should be made explicit in research protocols on adolescents so that ethics committees are aware of this.

Clear definitions of study populations and a sound understanding of local regulatory contexts will also inform decisions and actions on informed consent processes, as discussed in Section 2.
2.1 Introduction

Soliciting parental informed consent and a minor adolescent’s assent can be particularly challenging in the context of research on sexuality and reproduction. This section explores some of these challenges in the context of law and ethics. Individuals aged 18 years and over are usually treated as adults in their own jurisdictions and can give legally valid consent for themselves (assuming mental competency). In some settings, however, individuals are not treated as adults even though they have reached 18 years of age. Further, in some settings, cultural norms dictate that families may still expect to be involved in the decision-making process of an adult into the person’s mid-20s or even beyond.

2.2 Pertinent information necessary to resolve Case scenario 2

2.2.1 Children and decision-making

Article 12 of the CRC requires that a child who is capable of forming his or her own views must have the right to express those views freely in all matters affecting him- or herself, with the views of the child being given due weight in accordance with his or her age and maturity (16). The CRC presses

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Case scenario 2

A researcher intends to conduct a perceptions survey on sexual behaviour among adolescents in an urban community setting of a north African country. She is unsure of the following:

• whether to solicit informed consent or assent from study participants;
• what the notion of an adolescent’s capacity means for the requirements to obtain consent;
• whether she could apply for waiver of parental consent for special groups, such as street children.

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3 Autonomous participation in research takes into account not only age of majority but also mental competence. CIOMS defines competence or decisional capacity as “the ability to understand material information, appreciate the situation and its consequences, consider the treatment options, and communicate a choice. Persons should be considered capable of giving informed consent unless it is proven otherwise. A person may be incapable to give informed consent for a variety of reasons (for example, dementia, some psychiatric conditions and accidents)” (4).
for the right of children to have their voices heard, but this does not mean they have full autonomy. According to UNICEF, Article 12 “does not give children the right to autonomy. In other words, it does not give children the right to control over all decisions irrespective of their implications either for themselves or others” (61).

2.2.2 Autonomy

In the health context, autonomy is defined as the ability of a person to make an independent decision (without surrogate, parental or guardian assistance or approval). In most settings, children are not legally permitted to give consent to research participation autonomously, as their decision-making capacity is still considered to be evolving. Hence, only a child’s parent or legal guardian may legally provide consent for the child to participate in research. This decision-making process may well involve the child, depending on the nature of the research and the age of the child.

Although parents must provide legal permission for a child’s participation in research, there are important ethical requirements that must be ensured to respect a child’s own evolving capacity and autonomy. This is particularly the case in older children, who are more likely to understand research procedures and implications, and can decide whether or not to participate. However, legally, children can only assent to research participation until they are old enough to provide legally valid consent. In these cases, both the authorization or consent of the parents and the child’s assent or agreement must be obtained. Although similar in nature, informed consent and informed assent are distinct notions.

The CIOMS (4) and WHO (3) documents summarize two key conditions for a child’s or adolescent’s participation in research: permission by the child’s parent or legally authorized representative; and agreement (assent) from the child “in keeping with the child or adolescent’s capacity, after having been provided with adequate information about the research tailored to the child’s or adolescent’s level of maturity” (4).

2.2.3 Informed consent

In the research context, informed consent is the formal process for getting permission before a person can participate in research. As the therapeutic and research contexts are distinct from each other and involve different risks, the informed consent requirements and processes for both should not be confused. While many settings permit children limited or exclusive decision-making power in relation to particular treatment and care options available to them, in most settings, children (by definition, people who have not reached the age of legal majority) lack capacity to decide to participate in research and therefore cannot provide legally valid, autonomous consent (exceptions to this are discussed in Section 2.2.2 Autonomy). Instead, parental or guardian consent is a prerequisite to the child’s participation in research.

In summary, there are both legal and ethical requirements for consent:

- Legal requirements identify the people who can provide legally valid consent for a child’s participation in research – usually the child’s parents or legal guardians.
- Ethical requirements must also be considered. If a child has the capacity to make a decision concerning his or her involvement in research, then assent from the child as well as parental consent must be obtained. If a child does not have the capacity to decide upon participation in the research, then he or she should be appropriately involved in the decision so their voice is still heard (in order to uphold the rights outlined in Article 12 of the CRC). This process should be documented in line with any local requirements for “assent”.

Informed consent has four elements (62):

- Disclosure: the parent or guardian of a child research participant (and, where applicable, the child) must be provided with relevant information about the study, including its potential risks and benefits. Such disclosure should include informing the child of his or her privacy rights and limitations thereto, and the investigator’s disclosure obligations.

- Understanding: the parent or guardian (and, where applicable, the child) must appreciate and understand the information provided. Understanding may be compromised when the child is of a young age, lacks education or literacy, lacks the capacity to understand, or has a severe physical or mental illness affecting comprehension.

- Voluntariness: the parent’s or guardian’s permission to involve the child in research, and the child’s actual participation in research, should be free of coercion and be voluntary in nature.

- Capacity: the child’s parent or guardian must possess the decision-making ability to give permission for the child’s participation in research. According to CIOMS, decisional capacity or competence is determined by the “ability to understand material information, appreciate the situation and its consequences, consider the treatment options, and communicate a choice” (4). See Box 1 for considerations on assessing mental capacity.

In younger children, the cognitive capacity to understand what may be involved in a research study is likely to be limited. Older children, however, may have greater cognitive and decision-making capacity, and thus assent (see below) should be obtained until they reach the legal age whereby they can provide autonomous consent.

2.2.4 Assent

Individuals who are not legally able to provide autonomous informed consent may possess the ability to assent or dissent. UNICEF defines assent as “the willingness to participate in research, evaluations or data collection by persons who are by legal definition too young to give informed consent according to prevailing local law but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects” (63).

Assent is central to conducting research with children (including minor adolescents), as it gives them “the opportunity to be heard in any judicial or administrative proceedings affecting them, either directly, or through a representative or an appropriate body, in a manner consistent with the procedural rules of national law” as required in Article 12 of the CRC (16). Article 12 of the CRC designates that “children shall be assured the right to express their views freely in all matters affecting them, their views being given due weight in accordance with the child’s age, level of maturity, and what is in their best interest”. Thus, from an ethical perspective, if a child demonstrates decision-making capacity, the researcher should give due weight to the child’s views on his or her participation in research activities, regardless of the child’s legal capacity in the research setting, in accordance with Article 12.

In many settings, assent is not a legally recognized concept, although, as described above, it may be an ethical requirement or even an ethical imperative. Many settings that recognize the notion of assent do not specify a minimum age for this. Instead, this determination is left to the discretion of the local research ethics committees.
It is recommended that a child who is able to express his or her own view should be encouraged and enabled to do so by participating in the decision-making process. Any local requirements that specify how this should be achieved (e.g. by following a particular assent process to document the engagement process with the child) should be followed.

CIOMS considers assent to be a process, which is not simply the absence of dissent. In order for a child to give assent, he or she must be meaningfully involved in the decision-making process in a manner that is appropriate to the child's capacity and age. CIOMS outlines that assent processes "must take into account not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation" (4). Thus, it is important to know the child's thoughts, feelings and opinions in order to properly assess the impact of a proposed action on the child's welfare, even if the child lacks legal capacity to provide informed consent for the proposed action. Accordingly, age-appropriate and relevant study-related information (including what the study involves, and the associated risks and benefits) should precede the solicitation of assent from a child. While a child's cooperation in the research context may sometimes be a sign of implied assent, the child's failure to object to a research procedure or activity should not be interpreted as his or her agreement to participate. The forced involvement of the child in the absence of assent may constitute submission, which voids the apparent assent.

Assent may be expressed (e.g. indicated verbally or in writing) or implied or tacit (unspoken or implied through the individual's actions, for example by not making eye contact with the researcher or by remaining unresponsive to the researcher’s questions). Furthermore, a child has an ethical right to withdraw his or her assent. If a child expresses reservations about participating in research despite his or her parent or guardian consenting thereto, this does not necessarily equate to the child having the final say in the decision. Instead, enrolment or non-enrolment must be based on what is in the best interests of the child. This is a delicate matter and should be dealt with carefully.

In conclusion, there are three key considerations to be taken into account when approaching assent: the child's capacity to provide assent; any legal requirements on assent in the research setting; and the ethical requirements (or ethical imperative) to obtain assent. For instance, in the United States, the law requires particular assent processes to be followed, defining assent as the child’s affirmative agreement to participate in research (64). In determining whether a child is capable of assenting, the United States Department of Health and Human Services requires every institutional review board to take into account the age, maturity and psychological state of the child involved. If a child falls below the legal age of autonomous consent for research participation in a particular setting, then his or her agreement to participate in the proposed research should still be sought.

CIOMS outlines assent versus consent processes in adolescents nearing the age of majority as follows: “As adolescents near the age of majority, their agreement to participate in research may be ethically (though not legally) equivalent to consent. In this situation, parental consent is ethically best considered as ‘co-consent’ but legally, the adolescent’s agreement remains assent. If minor research participants reach the legal age of majority according to the applicable law and become capable of independent informed consent during the research, their written informed consent to continued participation must be sought and their decision respected” (4).
2.2.5 Maturity

In terms of the CRC, maturity refers to the ability to understand and assess the implications of a particular matter, and must therefore be considered when determining the individual capacity of a child. In the context of Article 12, it is the capacity of a child to express his or her views on issues in a reasonable and independent manner.

The notion of maturity also has sociocultural dimensions. In Bangladesh, for example, the age of maturity is considered to be 18 years, extendable up to 21 years, and is akin to the legal age of majority (when the person is deemed to be an autonomous adult). However, in terms of Hanifi law in Bangladesh, the age of maturity is 15 years, which is the notion used in the context of marriage, divorce and dowry (67).

Maturity also has health dimensions. Although there is no common definition of maturity among healthcare professionals, they generally subscribe to a developmental approach to maturity. The developmental approach, whether biological, psychological or social, views the child as a developing organism who progresses from one stage to another in a sequential manner (68). The developmental progression ranges from infancy through early and later childhood, to adolescence, early adulthood, late adulthood and old age. Particular developmental milestones and abilities accompany each developmental stage. These stages are often age-linked, but there are instances where these stages are attained outside the expected norm. Some children develop early (early developers), while others develop later (late developers). Various factors influence development, including gender, culture, the environment and resources.

In determining whether a child is mature enough to participate in research, or to consent autonomously in research, the ability, experience, degree of maturity, judgement and conduct of the minor should be considered (69,70). This may be needed because the child’s parent or guardian cannot be located and so the researchers consider seeking a waiver of parental consent, or because the child may wish to participate in research without their parents’ knowledge (see Section 2.2.6 Waiver of parental informed consent and Section 2.2.7 Waiver of documentation of informed consent). Furthermore, information provided to the child must be relevant, be in a format that is accessible, and give due consideration to the needs of disabled people, if applicable.

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**Box 1. Assessing a child’s capacity to assent**

In soliciting assent for clinical purposes, clear criteria are set to assess the capacity of a child. Assessment of a child's mental capacity to assent should consider the child's:

- ability to understand that there is a choice and choices have consequences;
- willingness and ability to make a choice, including the option of choosing that someone else makes treatment decisions;
- understanding of the nature and purpose of the procedure;
- understanding of the procedure’s risks and side-effects;
- understanding of the alternatives to the procedure and the risks attached to them, and the consequences of no treatment;
- freedom from pressure (65).

Dedicated guidance to assess a child’s capacity in the research context has been proposed (66).
Professions differ in how they interpret maturity. Table 1 summarizes the position of medical practitioners (71), psychiatrists (72), social workers (73), clinical psychologists (74) and lawyers (75) on this issue.

Table 1. Professional interpretations of “maturity”

<table>
<thead>
<tr>
<th></th>
<th>Medical practitioners</th>
<th>Psychiatrists</th>
<th>Social workers</th>
<th>Clinical psychologists</th>
<th>Lawyers</th>
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<td>Psychopathology Cognitive maturity</td>
<td>Experts</td>
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<td>Personality assessment</td>
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<td>Experts</td>
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<td>Abuse (physical, sexual)</td>
<td>Abuse (all)</td>
<td>Physical and psychological Abuse (all)</td>
<td>Physical and psychological Abuse (all)</td>
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<td>Violence and trauma</td>
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<td>MI</td>
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</table>

CA, chronological age; CI, clinical interview; IQ, intellectual functioning; MA, mental age; MI, medical interview; MSE, mental status examination; SI, social interview.

2.2.6 Waiver of parental informed consent

In some instances it may not be feasible to solicit permission from a parent or guardian for a child to participate in research. For example, in the case of a street child, the parent or guardian may be unknown, untraceable or deceased (see Section 1). In other instances – for example, for reasons of sensitivity, such as discussions about sexual activities, substance abuse, sexual abuse, physical abuse or neglect – it may be desirable and ethically justifiable for minors (especially minors aged 16 years and older) to choose independently (without parental assistance) whether to participate in research (76). In this regard, minors may be unwilling to participate in the proposed research if they are required to tell their parents or guardians about the nature of the research (77). In such circumstances, the researcher may consider applying to the governing research ethics committee for a waiver of parental or guardian consent. If the committee is not empowered to award such a waiver, as courts are generally regarded as the upper guardian of all children, then the researcher may consider petitioning a local court to grant such a waiver. In the United States, the governing institutional review board may waive the requirement for obtaining parental or guardian informed consent or approve a consent procedure that leaves out or alters some or all of the elements of informed consent (77). This can occur provided that:

- the research involves no more than minimal risk to the subjects;
- the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- the research could not practically be carried out without the waiver or alteration;
- whenever appropriate, the subjects are provided with additional pertinent information after participation;
- the research ethics committee or institutional review board determines that a research protocol is designed to study conditions in minors or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (e.g. those who have been neglected or abused), and an appropriate mechanism is in place to protect the subjects, and the waiver is not inconsistent with federal, state or local law (78).

In addition to the above considerations, it is advisable for investigators to engage with the host community or community representatives to seek their guidance on parental or guardian (or substitute) waiver processes. Such engagement should be documented and submitted to the governing research ethics committee in support of the proposed parental or guardian consent waiver process. The research ethics committees should base its decision on whether waiver is in the best interests of the child.

2.2.7 Waiver of documentation of informed consent

A waiver of documentation of informed consent entails obtaining consent from a child’s parent or guardian, without requiring them to sign a consent form. Implied consent or passive consent is a waiver of informed consent documentation. Before granting such a waiver, the research ethics committee or institutional review board may require the researcher to provide the participants and their parents with a written summary or an information sheet about the research, including the purpose of the research; the time involved; an assessment of risk; a statement regarding benefit to participants; a contact for questions about the research; and a contact for questions about rights as a research participant (79).
2.3 Case scenario 2 resolution

The researcher consulted with colleagues and made enquiries about the country’s regulatory regime to determine whether only parental or guardian consent must be solicited, or whether both parental or guardian consent and the adolescent’s informed consent or assent must be solicited (and the circumstances for this). The researcher also engaged with the host community to determine the social and cultural appropriateness of parental or guardian consent waiver in that setting, and sought community endorsement for such waiver. The researcher learned that the country’s laws confer the status of adulthood on individuals upon attaining 18 years of age, and that individuals over the age of 18 years can provide consent alone for their participation in the proposed research. For minor adolescents under the age of 18 years, however, the researcher discovered that the country had no legal requirements for assent. In consultation with the chair of the ethical review board at her institution, the researcher proceeded to solicit informed assent for minor adolescents in her study.

Further, based on discussion with members of the ethical review board, the researcher discovered that special requirements apply in her setting for minor adolescents who do not have access to a legal parent or guardian (e.g. street children in the study), or whose parents or guardians are unknown, untraceable or deceased. In these instances, the researcher learned that she should consider approaching a caregiver (if applicable and permissible) for such consent, or applying to the governing research ethics committee for waiver of parental or guardian consent. The researcher also learned that if the committee was not empowered to award such a waiver, she could approach relevant empowered officials (if applicable) for authorization, or the courts for a judicial order, for such a waiver.
Determine the country’s regulatory requirements with respect to informed consent, assent and capacity.

If the country lacks formal regulations pertaining to research with children, the permission of the parents or guardians should be solicited on ethical grounds before a child’s involvement in the research. The child's assent should also be solicited on ethical grounds.

If the country legally requires only the parent’s or guardian's permission for the child’s participation in research, the child’s assent should nevertheless be solicited on ethical grounds. A child who is able to express his or her view should be encouraged and enabled to do so, in line with Article 12 of the CRC. If a child expresses reservations about participating in research despite his or her parent or guardian consenting thereto, this does not necessarily equate to the child having control over the decision. Instead, enrolment or non-enrolment must be based on what is in the best interests of the child. Even if the child is deemed to lack capacity to make a decision about his or her participation in research and the parent or guardian has consented to the child's participation, the child should still be engaged and encouraged to participate in the decision-making process.

If the permission of the parent or guardian is legally required for the child’s participation in research but the researchers believe that such solicitation is not feasible or not in the best interests of the child, the researchers should apply to the governing research ethics committee for waiver of parental consent for the child's participation in the proposed research. If the country's regulatory system permits such waivers, the governing research ethics committee should grant such waivers only if doing so is in the best interests of the child (an individual child or a class of children at large and the investigator meets the requirements outlined in Section 2.2.6 Waiver of parental informed consent). If the governing ethics committee lacks such power, the researchers should apply to a relevant local court for such waivers, arguing that consent in this context is in the best interests of the child. In most countries, courts act as the upper guardian of children. Alternatively, the researchers should contact local health or research governance officials to determine whether designated government officials have the authority to grant such waivers.

### Box 2. Informed consent: summary recommendations

- Determine the country’s regulatory requirements with respect to informed consent, assent and capacity.
- If the country lacks formal regulations pertaining to research with children, the permission of the parents or guardians should be solicited on ethical grounds before a child’s involvement in the research. The child's assent should also be solicited on ethical grounds.
- If the country legally requires only the parent’s or guardian's permission for the child’s participation in research, the child’s assent should nevertheless be solicited on ethical grounds. A child who is able to express his or her view should be encouraged and enabled to do so, in line with Article 12 of the CRC. If a child expresses reservations about participating in research despite his or her parent or guardian consenting thereto, this does not necessarily equate to the child having control over the decision. Instead, enrolment or non-enrolment must be based on what is in the best interests of the child. Even if the child is deemed to lack capacity to make a decision about his or her participation in research and the parent or guardian has consented to the child's participation, the child should still be engaged and encouraged to participate in the decision-making process.
- If the permission of the parent or guardian is legally required for the child’s participation in research but the researchers believe that such solicitation is not feasible or not in the best interests of the child, the researchers should apply to the governing research ethics committee for waiver of parental consent for the child's participation in the proposed research. If the country's regulatory system permits such waivers, the governing research ethics committee should grant such waivers only if doing so is in the best interests of the child (an individual child or a class of children at large and the investigator meets the requirements outlined in Section 2.2.6 Waiver of parental informed consent). If the governing ethics committee lacks such power, the researchers should apply to a relevant local court for such waivers, arguing that consent in this context is in the best interests of the child. In most countries, courts act as the upper guardian of children. Alternatively, the researchers should contact local health or research governance officials to determine whether designated government officials have the authority to grant such waivers.

### 2.4 Conclusions

A researcher must prospectively vet the country’s regulatory framework for informed consent and assent in relation to children (including minor adolescents). A child’s participation in research should, where feasible, be preceded by an informed consent process with the child’s parent or guardian (or legally recognized alternative) and, where relevant, by an assent process with the child. Even where the child’s assent is not legally required for his or her participation in research, the researcher should nevertheless obtain the child’s assent on ethical grounds.
3 Reconciling conflicting ethical and legal obligations with regard to adolescent research participants

3.1 Introduction

The conduct of sexual and reproductive health research is fraught with legal and ethical challenges. These challenges are compounded with adolescent study participants, the majority of whom lack full autonomy to make decisions to participate in research. In some instances, researchers may also face apparent conflicts between their legal and ethical obligations in respect of adolescents.

Through illustrative case scenarios, two issues will be explored: when researchers are presented with a conflict between laws and ethics; and when the law is clear on an issue but presents significant risks to subjects.

Case scenario 3

A physician-researcher is conducting a study on HIV prevalence among adolescents and adults in a rural community-based setting in eastern Africa. As part of the study, all participants are subjected to anonymous HIV testing. Informed consent was solicited for all participants; parental consent and assent were solicited for minor adolescent participants in the study.

During the course of the study, several study participants were identified as having sexually transmitted infections. The treatment of sexually transmitted infections is not governed by the study protocol. Adult study participants identified as having sexually transmitted infections were referred to a local clinic. However, the country’s laws require the solicitation of parental informed consent before children (including adolescents under the age of 18 years) are put on any treatment.

In one particular case, the researcher informs an adolescent participant found to have a sexually transmitted infection that treatment is important for her health, but according to the country’s law her parents’ consent is required for treatment. The participant refuses to seek her parents’ consent, arguing that if they were to learn that she has a sexually transmitted infection, they will realize she is sexually active and, as a result, she could be punished. The participant informs the researcher that if she is forced to obtain parental consent for treatment, she will never return to the clinic and would rather remain untreated. The investigator is aware that he has an ethical obligation to ensure the adolescent receives treatment for the sexually transmitted infection. He is also aware that the adolescent is required by law to obtain parental consent for treatment. The researcher wants to do what is in the participant’s best interests. The investigator is unsure whether, in line with Article 12 of the CRC, he can proceed with treatment without parental consent.
3.2 Pertinent information necessary to resolve Case scenario 3

3.2.1 Legal and ethical obligations

Professional codes of conduct and laws generally govern the conduct of certain professionals. For example, in many countries, such as the United States (80) and India (81), health professionals are bound by a code of professional ethics. Transgressing such codes of conduct usually carries penalties enforced by the relevant governing professional council. Professionals may also be governed by specific laws. For example, health professionals and educators may have mandatory disclosure obligations in terms of child welfare laws that oblige them to notify authorities if they know or suspect that a child has been or is being abused. In such instances, the professional has an ethical obligation for confidentiality and a legal obligation to notify authorities of the abuse. It is important that researchers keep abreast of codes and laws pertaining to their professional conduct in relation to adolescents.

3.2.2 Managing conflicting legal and ethical obligations

As discussed above, researchers may have conflicting legal and ethical obligations. There is no consensus globally on how such conflicts should be managed (82). Some professional associations, such as the German Psychological Society (83), require their members to follow the law when there is an irreconcilable conflict between ethics and law. This is based on the principle that laws supersede professional codes of conduct, and both laws and professional codes of conduct supersede ethics guidance documents. Other professional bodies allow their members discretion in determining what to do when there is an irreconcilable conflict between ethics and law. For example, the American Medical Association advises its members that if they believe a law is unjust, they should work to change it – but in exceptional circumstances of unjust laws, the member’s ethical responsibilities should supersede legal obligations (84). The British Psychological Society advises its members to “analyse contradictions between law and ethics with particular care” and to “adhere to the extent possible to the ethical principles in its code while meeting the legal requirements of their professional roles” (85). The Canadian Psychological Association advises that if upholding ethical principles could “result in serious personal consequences (e.g. jail or physical harm) ... decision for final action would be considered a matter of personal conscience” (86). Many low- and middle-income countries do not have any national guidelines specifically addressing the ethical and legal challenges in sexual and reproductive health research with adolescents; recently, however, some countries, such as Kenya, have adopted such guidelines (87).

3.2.3 Acting in the best interests of the child

In some instances, researchers may find that the law or their governing professional code of conduct is silent on an issue. In such cases, researchers should act in the best interests of the child.

Article 3 of the CRC holds that the best interests of the child must be a primary consideration in all actions affecting children. Most countries have ratified the CRC. The term “best interests” broadly describes the well-being of a child. Such well-being is determined by a variety of individual circumstances, including the child’s age, the level of maturity of the child, the presence or absence of parents, and the child’s environment and experiences.
Several factors may be taken into consideration when determining the best interests of a child (Box 3) (88). Researchers should note that adolescents who are above 18 years of age are not governed by the CRC and may not be governed by local child laws if children in that setting attain the age of majority at the age of 18 years. In such instances, relevant laws that govern adults on the issue at hand should be considered.

**Box 3. Factors that may be taken into account when determining the best interests of the child**

In determining the best interests of a child (including minor adolescents), a researcher must identify what risks a child could be exposed to if an action is taken versus if an action is not taken. Researchers must evaluate the specific circumstances of each child to determine whether there are any such circumstances that could increase risks to the child’s health and well-being. Researchers must also evaluate whether study participation may jeopardize the child’s future in the short, medium and long term. Understanding the possible courses of action and the circumstances of the child, and making a judgement on what course of action causes least harm, are the central processes involved in determining the best interests of the child.

Useful considerations to keep in mind when determining the best interests of the child include:

- the child’s age, maturity, stage of development, sex, social background, and any other relevant characteristics;
- the child’s physical and emotional security, and their intellectual, emotional, social and cultural development;
- any disability that the child has;
- any illness that the child has;
- the need to protect the child from any physical or psychological harm that may be caused by:
  - subjecting the child to maltreatment, abuse, neglect, exploitation or degradation, or exposing the child to violence or exploitation or other harmful behaviour;
  - exposing the child to maltreatment, abuse, degradation, ill-treatment, violence or harmful behaviour towards another person;
  - any family violence involving the child or a family member of the child;
  - oppressive laws or state policies.


### 3.3 Case scenario 3 resolution

After checking the country’s laws and policies, the physician-researcher discovered there was no clear normative guidance pertaining to the treatment of a minor adolescent with a sexually transmitted infection without his or her parental consent. The researcher decided to consult with colleagues and a member of the local research ethics committee, who advised him that when the law is silent on a matter, or when adhering to the law could yield negative outcomes for an adolescent, the researcher should always act in the best interests of the adolescent. The rationale he was given was that although the CRC applies to individuals aged 18 years and under, the principle of acting in best interests applies to all research participants, including those over the age of 18 years.
The researcher considered the following options: (i) treat the minor adolescent on ethical grounds, while encouraging her to make a voluntary disclosure about her condition to her parent(s), guardian(s) or caregiver(s), which could hopefully translate to familial support; (ii) involve a third party outside the family to represent the minor adolescent; (iii) or withhold treatment. In this case, after further consultation with colleagues and reflection, the researcher decided to involve an adult who could act as an independent child advocate, in line with the guidance of CIOMS. The researcher’s reasoning was that the independent child advocate, the head of a reputed local nongovernmental organization working with young people, could represent the minor adolescent.

The researcher chose this course of action because soliciting the informed consent of the adolescent’s parents against the adolescent’s wishes would breach her right to confidentiality and may not be in her best interests. However, the researcher was cognizant that treating the minor adolescent without parental consent may have legal consequences. The researcher was mindful that disclosure obligations (e.g. if an adolescent acquired the sexually transmitted infection through sexual abuse) may, by necessity, have to override his ethical duty to the minor adolescent to maintain confidentiality. The reasoning for this is that disclosure to relevant authorities will usually be in the best interests of adolescents (e.g. may result in the removal of an adolescent from his or her abusive context). In such instances, the researcher was advised to treat the minor adolescent but also inform the child of mandatory disclosure obligations and the potential implications thereof.

The researcher made sure to report the case immediately to the principal investigator of the study and to the research ethics committee to discuss this case further and its implications on other cases.

In some instances, a proposed research study may be considered controversial if it focuses on a lifestyle or behaviour that is considered immoral and classified as unlawful in the local context. Such research is particularly fraught with challenges if it involves adolescent research participants.

**Case scenario 4**

Investigators in a southern African country want to conduct an open-label study to evaluate the uptake, adherence, safety and patterns of daily oral pre-exposure prophylaxis among HIV-negative young (aged 16–24 years) men who have sex with men and transgender women. However, homosexuality is a cultural taboo and is criminalized in the setting. What are the ethical and legal implications of conducting such research, and how should investigators proceed in this matter?
3.4 Pertinent information necessary to resolve Case scenario 4

The United Nations Committee on the Rights of the Child has noted:

“Adolescents who are lesbian, gay, bisexual, transgender and intersex commonly face persecution, including abuse and violence, stigmatization, discrimination, bullying, exclusion from education and training, as well as a lack of family and social support, or access to sexual and reproductive health services and information. In extreme cases, they face sexual assault, rape and even death. These experiences have been linked to low self-esteem, higher rates of depression, suicide and homelessness.”

Investigators should prospectively consider the implications of conducting research in settings with poor human rights records and where the focus of the proposed research (e.g. sexual behaviour in men who have sex with men) is criminalized. If conducting the proposed research in the setting is considered essential on public health and public interest grounds – notwithstanding the potential legal challenges implicit in conducting such research – investigators should precede the proposed research with meaningful engagement with the study site’s local community and civil society, and with health and social services, justice (prosecuting) authorities and law enforcement authorities. Doing so will help investigators understand the consequences of such research in the context and how the researchers and study participants will be perceived. This also applies to research in settings where the legal age of sexual consent is above the study’s proposed threshold age inclusion criteria.

If authorities cannot guarantee that the study participants and the staff conducting the study will not face state-endorsed discrimination, harassment, victimization, criminal sanction or barriers in obtaining support services, and that confidential study records will not be subject to search and seizure, then the researcher should reconsider conducting the proposed research in that setting. However, the investigators should continue lobbying for changes in local law and policy to alleviate the conditions understood to be associated with the proposed study cohort.

3.5 Case scenario 4 resolution

In this case, the investigators determined there were no guarantees that research study staff and participants would not be subjected to criminal sanction, and thus they decided not to proceed with the study. This decision was reached after considering carefully what course of action would protect and ensure the best interests of the research participants in the proposed study setting.

However, the investigators were advised by colleagues that should the necessary guarantees be obtained in the future, they should give careful thought to potential social harms and pay particular attention to confidentiality and disclosure obligations (Box 4) and informed consent procedures.

In moving forward, the investigators sought to better understand how to obtain the necessary guarantees to support research studies with men who have sex with men and transgender people in the future. Through forming partnerships with local organizations and authorities, they began efforts to advocate for change.
In instances where a researcher finds that adherence to the law potentially conflicts with their professional code of ethics, they should reflect on these instances, consult with colleagues, and, based on their advice, seek the most ethical course of action and the most responsible, knowledgeable, effective and respectful way to carry it out (86).

The solicitation of parental consent in instances where research participants are deemed minors under domestic law will inadvertently breach the confidentiality of participants with respect to issues such as their sexual orientation and sexual behaviour, which may trigger social harms. In such instances, investigators are advised to consider exploring whether local law or research regulations permit governing research ethics committees to waive parental consent.

If study participants disclose during the course of a study that they are engaging in sexual activity below the host country’s legal age of sexual consent, such conduct may trigger disclosure obligations to relevant authorities on the part of investigators. Investigators should devise appropriate standard operating procedures to manage such instances. They should also consider devising risk mitigation plans to manage potential social harms. To this end, investigators should consider constituting a rapid response committee to manage difficult situations when they arise. Ideally, the team should comprise representatives from the research team, the legal profession, the community, and the relevant authorities (including members from law enforcement, the judicial sector, and health and social services).

### Box 4. Resolving ethical and legal obligations: further recommendations

In instances where a researcher finds that adherence to the law potentially conflicts with their professional code of ethics, they should reflect on these instances, consult with colleagues, and, based on their advice, seek the most ethical course of action and the most responsible, knowledgeable, effective and respectful way to carry it out (86).

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### 3.6 Conclusions

Researchers should avoid conducting research in settings where the subject matter of the proposed research is unlawful and where authorities are not supportive of the proposed research. Although research studies should be avoided in these settings, it is important that researchers, research organizations and governing research ethics committees make efforts to advocate for change.

If a researcher carrying out a study with adolescents encounters a conflict between a legal obligation and an ethical duty, the researcher should obtain advice from their governing professional association on how such a conflict should be managed. Should the governing research ethics committee offer no guidance on the issue, or offer guidance contrary to the interests of the adolescent, then the researcher should always act ethically, which in the context of an adolescent would require the researcher to act in the best interests of the adolescent. In such instances, the researcher needs to be cognisant that their actions or omissions may carry legal implications.
4.1 Introduction

Children, including minor adolescents, have rights related to information-sharing by virtue of the CRC. These rights provide helpful guidance to researchers who may be faced with information-sharing dilemmas.⁴

4.2 Pertinent information to resolve Case scenario 5

Children and adolescents below the age of 18 years have several rights that pertain to information-sharing that are relevant to consider when they participate in research. These include the child's right to share information, to be informed about pertinent issues, to have access to information, and to privacy. As noted earlier, adolescent participants who are over 18 years of age are not governed by the CRC and may not be governed by local child laws if children in that setting attain the age of majority at the age of 18 years. In such instances, relevant laws that govern adults on the issue at hand should be considered. The following sections deal with adolescents who are younger than 18 years, referred to as “children” in the CRC.

4.2.1 The child's right to share information, and to freedom of thought, conscience and belief

Article 12 of the CRC assures a child who is capable of forming their own views the right to express their views freely on matters that pertain to themselves. Article 14 requires that the right of the child to freedom of thought, conscience and religion be respected. To this end, the rights and duties of the parents and, when applicable, legal guardians to provide direction to the child in the exercise of their right in a manner consistent with the evolving capacities of the child must be respected. Such rights may become relevant during the informed consent and assent processes. Should a child express

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⁴ CIOMS outlines information-sharing guidance in the context of research with adults (4).
reservations about participating in a study or study procedure following relevant counselling, the child’s views must be given due weight in accordance with his or her age and maturity.

4.2.2 The child’s right to be informed

Researchers may discover sensitive information related to child study participants during the research process. This includes information relating to a child’s health status or prognosis. Researchers may be faced with a dilemma if the child’s parents or guardians do not want the child to be informed of this information. While researchers should be guided by the wishes of the parent or guardian, they should always act in the best interests of the child. Depending on the child’s age and level of mental maturity, the best interests of the child may necessitate the child being informed of their health status or prognosis. Researchers should consider Article 13 of the CRC, which provides that subject to certain restrictions contained in law and that are deemed necessary, the child has the right to seek, receive and impart information and ideas of all kinds, regardless of frontiers, either orally, in writing or in print, in the form of art, or through any other media of the child’s choice.

4.2.3 The child’s right to have access to information

Article 17 of the CRC recognizes the function performed by the mass and other print media and provides that the child must have access to information and material from a diversity of national and international sources, especially those aimed at the promotion of their social, spiritual and moral well-being and physical and mental health. This right should be taken into account when study-related material is being compiled for the child.

4.2.4 The child’s right to privacy

Article 16 of the CRC stipulates that no child must be subjected to arbitrary or unlawful interference with their privacy or correspondence. However, despite this right, the child’s right to privacy is not necessarily inviolable.

Researchers may encounter sensitive information about a child in the course of their interactions with that child. This information may be disclosed directly by the child, or it may emerge indirectly, for example during a medical examination. Researchers should usually treat such information as confidential. In some instances, however, the information may need to be shared with other relevant people as it may be in the best interests of the child to do so. For example, the disclosure of the child’s situation to a relevant party could help to protect the child from harm and ensure they get the help they need. In such instances, depending on the nature of the information, the researcher should encourage the child to make a voluntary disclosure of the information to their parent or guardian.

If the child refuses, or if it is not practical to ask for consent to disclose the information to other relevant parties, the researcher should consider the benefits and possible harms that may arise from the disclosure. In particular, the researcher should consider any views given by the child as to why the information should not be disclosed to other people. In coming to a decision on the matter, researchers must be guided by what is in the child’s best interests. Examples of when involuntary disclosure may be necessary include if the child has a serious illness (e.g. clinical depression) and requires a medical intervention, or if the child is involved in behaviour that might put him or her or others at risk of serious harm (e.g. suicidal ideation, intention to harm someone), or if the child is at risk of neglect or abuse. If involuntary disclosure is deemed justified, the researcher should disclose the
information promptly to an appropriate person or authority and record the reason for the disclosure and discussions with those parties.

If the researcher deems disclosure to be unwarranted, he or she should record the reasons for not disclosing the information to other pertinent parties. In some instances, involuntary disclosure to the parent or guardian may not be in the child’s best interests (e.g. if the child discloses to the researcher that he or she has been abused and that the parent or guardian is the perpetrator of the abuse or is shielding the perpetrator of the abuse). In such instances, the researcher should not breach the child’s confidentiality to the parent or guardian but should make a disclosure to the relevant authorities. If the researcher is contemplating breaching the child’s confidentiality, the researcher should record their discussions with the child and the reasons for sharing the information. Researchers should disclose information as required by law and when directed to do so by a court.

4.3 Case scenario 5 resolution

Following a thorough consultation of CRC laws, the organization decided to use the CRC as the foundational basis to guide the development of its policy on information-sharing with adolescents. As the organization works with individuals who are both over and under 18 years of age, the organization ensured its policy would be based on broad principles, while taking into account the fact that children under 18 years of age are governed by the CRC, but people over 18 years of age are governed by different laws (89). In putting forth the following five guiding principles, the organization checked relevant privacy and data-sharing laws, policies and ethics guidance documents, and consulted with key informants, as they provided a helpful framework to ensure personal information is shared appropriately:

- The researcher must base information-sharing decisions on considerations of the safety and well-being of the adolescent and others who may be affected by such actions. The researcher should seek advice if they are in any doubt, without disclosing the identity of the adolescent, where possible.

- The researcher must be open and honest with the adolescent (and his or her parent, guardian or caregiver, where appropriate) from the outset about why, what, how and with whom information will or could be shared, and seek the adolescent’s (and, where applicable and appropriate, the parent’s, guardian’s or caregiver’s) agreement to make such disclosure, unless it is unsafe or inappropriate to do so. In some instances, researchers may have mandatory disclosure obligations to relevant parties. Adolescent study participants and their parents, guardians or caregivers should be informed about this during the informed consent process at study enrolment.

- The researcher must ensure the information they share is necessary for the purpose for which they are sharing it, is shared only with people who need to have the information, is accurate and up to date, is shared in a timely fashion, and is shared securely.

- The researcher must share any information about the adolescent with his or her consent. The researcher may share information without consent if, in their judgement, lack of consent can be overridden in the adolescent’s interest or in the public interest. The researcher needs to base their judgement on the facts of the case.

- The researcher must keep a record of the decision and the reasons for it – whether that is to share information or not. If the researcher decides to share the information, they must record what was shared, with whom, and for what purpose.
4.4 Conclusions

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 their best interests. Research organizations are advised to devise policies or standard operating procedures to govern information-sharing in respect of their study participants. Such an approach will facilitate a timely and uniform response to dilemmas if, and when, they arise.
Adolescents have unique health needs, experiences and challenges, and it is crucial to include them in research. However, research with adolescents is fraught with ethical and legal challenges, particularly in the context of sexual and reproductive health. As adolescence is a critical period of physical, psychological and social development, characterized by evolving decision-making capacity and independence, there are important protections, processes and considerations to be made when involving adolescents in research. This guidance document outlines the terminologies used to describe different groups of adolescents, the notions of autonomy, consent and assent, the implication of best interests to reconcile ethical and legal obligations, and some best practices surrounding information-sharing in the context of sexual and reproductive health research with adolescents.

Through the illustration of paradigmatic case scenarios, this guidance document is intended to highlight some of the most common challenges faced by people involved in adolescent research, and how such challenges may be managed. As with most guidance documents, the proposed recommendations are not intended to be definitive or exhaustive. Notwithstanding the guidance offered in this document, people involved in research with adolescents should always exercise their discretion in resolving ethical and legal challenges, taking into account their personal knowledge of the issues at hand, the personal circumstances of the adolescent, and the prevailing cultural, political, legal and socioeconomic milieu of the study setting. Beyond all, people involved in research with adolescents should always strive to act in the adolescents’ best interests.

The participation of adolescents in sexual and reproductive health research is vital to better understand and address the needs of this unique group. In order to ensure the health and well-being of adolescents, and their ability to thrive, high-quality research in adolescent sexual and reproductive health is essential to fill gaps in data and inform successful programmes and policies. This guidance document aims to inform the appropriate involvement and protection of adolescents in research, because ultimately adolescent health and well-being depend on it.
Glossary of terms

This glossary provides definitions for common concepts, principles and values in health ethics. Several definitions are available for many of the terms listed. As a result, the summary is not intended to be definitive but rather as an aid to understanding common terminology. Each entry was developed by drawing on definitions provided in complementary documents and ethical codes pertaining to research involving people.

Assent

“The willingness to participate in research, evaluations or data collection by persons who are by legal definition too young to give informed consent according to prevailing local law but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects” (63).

“Assent is a process, and in order to obtain assent, the child or adolescent must be meaningfully engaged in the research discussion in accordance with his or her capacities. The process of obtaining assent must take into account not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation” (4).

Autonomy

“The ability of a person to make an independent decision (i.e. without surrogate, parental, or guardian assistance or approval)” (15).

As defined in the Belmont Report, the ethical principle of respect for people requires that people should be treated as autonomous agents, and people with diminished autonomy are entitled to protection. The Belmont Report defines an autonomous person to be an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. Respecting autonomy means that the autonomous person's opinions and choices are given weight, while refraining from obstructing their actions unless they are clearly detrimental to others. The Belmont Report notes that the capacity of self-determination matures during a person's life, and respect for immature people may require protecting them as they mature. The judgement that any person lacks autonomy should be re-evaluated and will vary in different situations (15).

Benefit

“To refer to something of positive value related to health or welfare. The ethical principle of beneficence requires that possible benefits are maximized and possible harms are minimized to research participants” (15).
The Belmont Report states that unlike “risk”, the term “benefit” does not express probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. In keeping with the principle of beneficence, research must be justified on the basis of a favourable risk/benefit assessment. Risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Researchers must ensure that risks to subjects are minimized and outweighed by the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research (15).

**Best interests of the child (also known as “best interests”)**

“Broadly describes the well-being of a child. The best interests of the child, defined by the, is a substantive right, a legal principle, and a rule of procedure” (90).

“Article 3 of the United Nations Convention on the Rights of the Child gives the child the right to have their interests taken into account as a primary consideration in all actions and decisions concerning them, in both the public and private spheres. Assessing the best interests of a child should take into account a variety of individual circumstances, such as the child’s age, the level of maturity of the child, the presence or absence of parents, and the child’s environment and experiences. In making a determination about the best interests of the child in the research context, the researcher must evaluate the impact (positive and negative) of the decision on the child or children concerned” (90).

**Confidentiality**

“The obligation to keep information private unless its disclosure has been appropriately authorized by the person concerned or, in extraordinary circumstances, by the appropriate authorities” (91).

**Ethics (ethical standards)**

Ethics is concerned with questions about right versus wrong conduct and the justification for such questions. The establishment of ethical principles or standards for research with human beings can be traced back to the Nuremberg Code, which was developed after the war crimes trials of Nazi doctors in Nuremberg in 1947. Several subsequent international ethical guidelines, codes and statements pertaining to research have since been released, such as the Declaration of Helsinki (92), the International Ethical Guidelines for Health-related Research Involving Humans (4), and the Casebook on Ethical Issues in International Health Research (93).

**Guardian/guardianship (of a minor)**

“An individual or entity that has the legal authority and responsibility to care for a minor. In the research context, a legal guardian can provide consent for a child’s participation in research” (94).

**Harm**

“To refer to negative consequences arising from participation in a research study. Types of harm can include physical harm, psychological harm, social harm, legal harm, and economic harm. Harms can be minor or serious in nature. The likelihood that a research participant will experience harm and the severity of the potential harm constitute risk” (95).
Human rights
“The basic rights and freedoms to which all humans are entitled, whatever one’s nationality, place of residence, sex, national or ethnic origin, colour, religion, language, or any other status. These rights are all interrelated, interdependent and indivisible. Universal human rights are often expressed and guaranteed by law, in the forms of treaties, customary international law, general principles and other sources of international law. International human rights law lays down obligations of Governments to act in certain ways or to refrain from certain acts, in order to promote and protect human rights and fundamental freedoms of individuals or groups” (96).

Informed consent
“The formal process of making a free and informed decision to participate in research. Informed consent must be provided by a legally competent individual who has received information about the study including its potential risks and benefits; who understands the information provided; and who has arrived at a decision without coercion. In most cases, minors cannot provide legally valid informed consent; instead, parental/guardian consent is required for the minor’s participation in research. Nonetheless, if a minor is able to give assent, the researcher must seek the minor’s assent in addition to the parental/guardian consent” (92).

Law (legal standards)
“Principles and rules of human conduct, which are prescribed or recognized by the governing power in a society” (97).

“Laws and ethics can be complementary to one another or conflicting. Many countries have enacted legal regulations pertaining to ethical conduct in research involving human subjects. One such regulation is the United States Federal Policy for the Protection of Human Subjects” (64).

Privacy
“The right of individuals to limit access by others to aspects of their person that can include their thoughts and identifying information” (63).

Privacy is also a right, as recognized by the United Nations Convention on the Rights of the Child, which gives children the right to privacy. Article 16 of the CRC stipulates that no child must be subjected to arbitrary or unlawful interference with their privacy or correspondence, or to attacks on their honour and reputation. However, despite this right, the child’s right to privacy is not necessarily inviolable. In some instances, it may be in the child’s best interests for confidential information to be disclosed to his or her parent or guardian in order to protect the child from harm and ensure they get the help they need.

Professional code of conduct
Professional codes of conduct generally govern the conduct of certain professionals. In many countries, health professionals are bound by a code of professional ethics. Transgressing such codes of conduct usually carries penalties enforced by the relevant governing professional council.
**Research ethics committee or institutional review board**
A group of individuals who undertake the ethical review of research protocols involving humans, applying agreed ethical principles (91).

**Risk**
“Generally understood as an estimate of two factors: first, how likely it is that a participant will experience a physical, psychological, social or other harm; and second, the magnitude or significance of the harm. This understanding of risk implies that discomfort, inconvenience or burdens are harms of a very small magnitude that are almost certain to occur during research” (4).

**Study protocol (also known as “research protocol” or “protocol”)**
A document that justifies the background, purpose, rationale and objectives of the research study and describes all aspects of study organization and performance, including study design (including sample population and inclusion and exclusion criteria), methodology, safety considerations, follow-up activities, data management and statistical analysis, dissemination of results, and ethical considerations (92,98).


31. Indian Majority Act, Act No. 9 of 1875 (1875).


59. 21 C.F.R. 50 §50.3(a) (2017).

64. Requirements for permission by parents or guardians and for assent by children, 45 C.F.R. §46.408 (2009).


75. Gillick v. West Norfolk and Wisbech Area Health Authority (AHA) AC 112 (1986).


77. General requirements for informed consent, 45 C.F.R. §46.116(c), §46.116(d) (2009).

78. Requirements for permission by parents or guardians and for assent by children, 45 C.F.R. §46.408(c) (2009).


98. Recommended format for a “research protocol”. Geneva: World Health Organization (http://www.who.int/ethics/review-committee/format-research-protocol/en/).