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Including adolescents of child bearing potential in clinical trials or exposure to teratogenic medication: a guide

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This guide provides a concrete guidance as how to respond to the situation of minor adolescents of Child Bearing Potential (CBP) who may be enrolled in a clinical trial and/or need to receive potentially teratogenic medication. It advises on how to deal with the issue of adolescents of CBP in regards to the prescription and maintenance of contraceptives as well as the use of pregnancy test. It gives suggestions as how to react to the adolescent who claims/needs confidentiality. It offers a tool on how to assess an adolescent's functioning and lifestyles.

Objectives

The issue of contraception and pregnancy among women participating in clinical trials (whether healthy females or individuals suffering from a disease) is an important topic, given the potential harmful effect of various therapeutic procedures tested. As stated by the European Medicines Agency «precautions to prevent pregnancy include pregnancy testing (e.g. based on the β-subunit of HCG), use of highly effective methods of birth control and study entry only after a confirmed menstrual period, and in most instances, protocols require the use of an effective contraception during the trial and for some time after completion of the trial, among females, in several occurrences among males or partners as well»[1]. In other terms, most protocols for investigational drugs stipulate that Women of Child Bearing Potential (WoCBP) must use a recognized method of contraception and commonly specify a combination of chemical and barrier methods.

The issue of minor adolescents of childbearing age is difficult to deal with, given the young person's rights for confidential care and the obligation to adopt the same protection standards as those used for adult individuals. While swissethics has recently issued a brochure on how to deal with clinical trials among healthy children and adolescents[2], this brochure does not provide any specific guidance regarding the issue of reproductive life. Interestingly, other documents pertaining to the involvement of adolescents in research and clinical trials do not mention how to concretely handle the issue of sexual life and minors of Child Bearing Potential (CBP)[3-5]. Moreover, protocols are not always explicit as how to deal with this matter.

The objective of this document is to provide concrete guidance as how to respond to the situation of minor adolescents of childbearing age who may be enrolled in a clinical trial. To much extent, the content of this document, based on available publications[3,6-9] also addresses the topic of prescribing medication or procedures that are licensed by Swissmedic but have a teratogenic potential. The legal and ethical issues linked with this situation are described in details in annex 1.

Adolescent sexual and reproductive health

Any female adolescent who has a pubertal development at Tanner stages 3 to 5 is potentially able to become pregnant. Assessing Tanner stage is usually not difficult[10,11], either by direct examination or using drawings of the five stages or asking questions (adolescent's self-assessment[1], see annex 4)[12]. Indeed, while pregnancy can theoretically occur by Tanner stage 3 (e.g. around the age of 10-12 years for most girls), one should remember that the majority of adolescents do not engage in intimate sexual activities, including active/penetrative sexual intercourse before the age of fifteen, sixteen or later. As a matter of fact, according to the most recent available data[13], in Switzerland, the mean age for first sexual intercourse is 16.4 years among boys and 16.7 among girls.

As many trials last for several years, researchers including very young adolescents in a research should not forget that any adolescent could engage in sexual intercourse some time over the duration of the trial. This is all the more important to keep in mind as the young persons' behaviors are often unexpected and unpredictable[14,15]. In addition, while many professionals think that adolescents with a chronic condition do not engage in exploratory behavior (such as using drugs or having sex), this is wrong: young people with chronic conditions do adopt such behaviors as much or even earlier than their healthy peers[16-18]. In other words, an abstinent adolescent at the inclusion

[1] The adolescent may make a self-assessment based on the drawings of the Tanner stages if the direct examination by the doctor is not appropriate or is not accepted. (annex 4)

in a clinical trial may become sexually active over time, a situation that needs to be regularly monitored.

Moreover, as sexual experiences are sometime not disclosed to the parents/ caregivers, at least initially, this information must be gathered in a secured, empathetic and confidential atmosphere[19]. Such confidential care is granted to any adolescent who is considered competent, meaning able to reflect appropriately and make autonomous decisions[3,8,20,21] (see annex 2). At the same time, for many parents or guardians, raising the issue of a contraception requirement comes as a shock and may deter them from giving permission to participate in the trial. Thus, this situation must be handled with sensitivity.

Clinical trials with minor children of childbearing potential (CBP)

Most protocols for investigational drugs stipulate that women of CBP must use a recognized method of contraception. They usually request pregnancy tests and the use of a combination of chemical and barrier methods; moreover, abstinence is most of the time not acceptable. The parents of a CBP adolescent involved in a clinical trial should be made aware of such protective measures.

Any competent adolescent should benefit from confidential care if asked for. In Switzerland, with regards to the purpose of research, it is legally admitted within the Human Research Act (HRA) that from the age of 14, an adolescent is competent and able to make autonomous decision. However, it may apply to younger adolescents especially when confidentiality is needed to explore the young person's lifestyles; it may as well not apply to some adolescents above 14 years of age who lack the cognitive and affective characteristics of competence (annex 2). Lastly, all professionals engaged in clinical trials involving CBP should be aware of the fact that the meaning of sexuality and of adolescent sexual behavior differs widely from one culture or religion to another[22,23]. Thus, the issue of contraception must be discussed in a respectful atmosphere and the investigator should carefully explore the adolescents' and the parents' views.

This means that for young adolescents, even not necessarily fully competent, information about sexual behavior should first be gathered in a confidential way, outside the presence of the parents. If an adolescent discloses active/penetrative sexual intercourse without the parents knowing, she should undergo a pregnancy test. Confidentiality could be maintained at least for a while and *as long as the adolescent can be considered as competent,* but in all circumstances, the adolescent should be *strongly* encouraged to disclose her situation to her parents or caregivers, especially if she is young (e.g. under 14 years of age). If the adolescent still refuses, parents might be notified that a contraception is routinely part of the protocol even for abstinent adolescents, or the adolescent should be removed from the trial. Importantly, many trials last for several months or years, so that the sexual activity of the adolescent should be frequently reviewed (e.g. every 1-3 month).

Tackling the situation of the adolescent

Assessing the adolescent's competence

The HRA sets the limit between childhood and adolescence at completed 14 year of age. However, given the broad range of cognitive and affective development among children, this does not mean that individuals younger than 14 years are not competent, nor are all individuals older necessarily competent in all situations. The assessment of adolescent competence (decision-making capacity) is a process that should be carefully conducted, often over more than one encounter (annex 2)[8]. Moreover, this evaluation should be conducted in the light of the situation: it is indeed different to provide confidentiality for an interview on lifestyles or for the decision to undergo an abortion or to continue a pregnancy. Research collaborators who are not used to perform such an assessment should ask for the support of senior experienced colleagues with some training in adolescent medicine.

Delivering the information to the parents

The information should be as comprehensive as possible, and parents should be encouraged to understand why a specific protocol requires a thorough review of the adolescent's lifestyles, including the issues of the adolescent's vision of the disease, the adherence to treatment, and more broadly health issues, lifestyles and exploratory behavior. The parents should know that there is a need to explore sexual behavior and, in some instance, to provide contraception and perform pregnancy tests. They should also be encouraged to understand why it is important, during this period of life, to have a discussion with the adolescent alone, keeping in mind that the adolescent will be encouraged to disclose most/ all the content of the confidential exchange. This procedure could be presented as a "routine", to avoid angry reactions from the parents; it should as well be expressed and discussed while taking into account the cultural and religious background of the family.

Delivering the information to the adolescent

As reminded in the above mentioned guide on health research among children[2], the information regarding the trial should be delivered in a way that is appropriate to the adolescent's developmental stage and cognitive skills. It is not acceptable to provide such information in a kind of "top-down" attitude; rather, the health care professional should ask the adolescent to reformulate with her own words what has been understood[2,6,24,25]. The adolescent should be encouraged to disclose her vision of the situation, ask questions about her illness, the treatment/ trial and the prognosis[7,19,26-28]. This approach is closely linked with the evaluation of competence, of the capacity to make autonomous decisions.

Evaluating the adolescent's situation and lifestyles, including sexual behaviour

The clinical care of any adolescent requires a review of his/ her lifestyles[29], covering topics such as living conditions, leisure and sports activity, social network, mental health, substance use, as detailed in annex 3. It is usually not difficult to obtain credible answers in the field of sexual behavior, as long as confidentiality is ensured; in addition, the reasons why these questions are raised should be carefully explained.

The assessment should be emphatic, non-judgmental and progressive, starting with inquiries around puberty, menstruations, opinions regarding sexuality and progressively moving on more intimate matters with straightforward questions such as (see annex 3):

- "Some girls at your age have sexual experience or intercourse, do you know of such situations?"
- "What about you?"
- "Have you ever had a sexual experience?"
- "How do you feel about having sex?"
- "Did you already have a sexual intercourse?
- "When do you imagine that it would happen?"
- "What would you do if you are asked to or have had a sexual intercourse?"

The questions should not be provided as a kind of checklist, but rather be brought according to the adolescent stage of development and cognitive capacity.

How to make decisions regarding the involvement of adolescents with CBP

The ***algorithm*** on annex 5 offers a systematic procedure as how to respond to different types of situations, knowing that adolescents can move quickly from one to another, so *that the procedure should be repeated over time*: every 3 months, or even more frequently according to the protocol, to the pubertal stage of the adolescent and to her psychosocial situation). The procedure can be run by the principal investigator, one of the researchers or a specially trained health professional as defined in the protocol. *This person should be identified prior the beginning of the study*.

- First, one needs to assess the Tanner stage of the adolescent. This is part of the usual assessment of the adolescent's situation that has to be maintained over the whole duration of the trial or treatment[2]. Annex 4 provides a description of the five Tanner stages.
- Next, the health professional needs to investigate in a confidential setting (at least when dealing with intimate matters) the lifestyle of any adolescents above Tanner stage 2, as described before and in annex 3. To much extent, this procedure can also be applied to adolescents Tanner stage 1 and 2, as it helps the researcher to anticipate future issues in the field of lifestyles and sexual behaviour; but of course, the content of the review must be adapted to the adolescent's cognitive and affective stage.
- For adolescents Tanner 1 or 2, or not disclosing *any* current or foreseen heterosexual activity, it may be acceptable to rely on abstinence, as long as it is made clear that the issue of sexual behavior will be monitored on a regular basis. However, abstinence is only a possible option if the adolescent is clearly able to judge the risks of pregnancy under research.
- If the adolescent is more than Tanner stage 2 and does not seem reliable, or if the adolescent is considering sexual activity in the near or middle-term future, or if she discloses a sexual activity (e.g. intimate exchanges, sexual intercourse) a pregnancy test should be performed[3]. This can be presented as a routine, to avoid concerns or "outraged" reactions from the parents or the adolescent.
- If the test is negative, the adolescent should be asked to consult a gynaecologist, a specialist already known, or, better, a specialized adolescent gynaecologist, to investigate further the situation and decide if, and what contraception can be offered and promoted[30]. As adherence to oral contraception (OC) is often sub optimal during adolescence, alternatives to the use of OC or condom should be proposed upfront, such as long-acting contraception[31-34], that offers greater security (e.g. injectable, IUDs, implants). As it is the case for older women, periodic abstinence (e.g. using calendar, ovulation, symptom/ thermal, post ovulation methods) and withdrawal are not acceptable. If OC is kept as an alternative, remember that, even if it does not affect fertility, contraindications should be reviewed by the gynaecologist. Moreover, the decision should be made in collaboration with the research team, as some medication (including those prescribed as part of a clinical trial) interfere with OC.
- In some instances, the adolescent may not agree to disclose to the parents that she is sexually active. This is in principle acceptable for competent adolescents especially if 14 years of age or older (annex 2). If the adolescent remains opposed to such a disclosure, and depending on her age, one option is to tell the parents that contraception is required by the protocol (with regular pregnancy tests), and the other is to remove the adolescent from the trial. Keep in mind the fact that, in a very limited number of situations, disclosing the sexual activity of an adolescent to parents belonging to a strong religious community may lead them to send back the adolescent to the country of origin, enforce a marriage, or entail severe physical punishment and/or psychological abuse.
- Apart from the rare special circumstances just described above, sexually active adolescents, especially those under the age of 14, should be strongly encouraged to disclose to their parents the fact that they are sexually active: this is a situation that requires specific skills and that should be dealt with either by the gynaecologist or a trained researcher or collaborator of the health care team. It often takes some time to convince the adolescent to do so.
- If the pregnancy test turns out to be positive, the parents should, with very few exceptions, be informed of the situation, and the discussion will be the same as it would be for any adolescent facing an unexpected pregnancy[35-37]. Again, research collaborators who are not used to deal with such situation should ask for the support of senior experienced colleagues with some training in adolescent medicine. The adolescent should not be involved in the trial, or be withdrawn from an ongoing trial and be sent to a gynaecologist and a social worker to discuss the issue of keeping the pregnancy or undergoing abortion. Nearly all such situations should be discussed with the parents/ caregiver – and, if possible, with the male partner. In

[2] The adolescent and the parents should understand that this is part of the assessment of the situation and represents an opportunity to clarify issues related to the subject's health in general, and to the disease/ medication/ trial.

[3] Especially fully developed female adolescents are statistically more likely to become sexually active because they are more often together with older adolescents.

rare instances, with an adolescent displaying full competence, and if disclosing the pregnancy to the parents bears extensive potential risks for the physical or psychosocial health of the young woman, abortion can be performed with the support of a social worker or another trusted adult without the parents knowing. In Switzerland, most unexpected pregnancies end up with an abortion[37]. An enrolment of the adolescent in the trial after having had an abortion is open to discussion, but evidently should be considered only with an effective contraception, preferably of long-acting reversible type (IUDs, injectable, implants).

- If the pregnancy is continued, teratogenic therapies must of course be immediately terminated, or the adolescent should not be included in the trial.

Annexes to this guide

Annex 1: Minor adolescents' rights and ethical issues

Annex 2: Assessing the adolescent's competence

Annex 3: Review of the adolescent's lifestyles: the HEEADSSS approach

Annex 4: References

Annex 5: Tanner stages (adapted from Tanner J, 1962

Annex 6: Algorithm on how to deal with medication prescriptions to adolescents with CBP

ANNEX 1: Minor adolescents' rights and ethical issues

Over the last two or three decades, minor children and adolescents have become more and more actively involved in decisions affecting their health and life[25,38,39]. This trend is linked with important initiatives and documents issued, among others, by the United Nations and the World Health Organization[21,40,41]. In tackling those issues, the health practitioner should keep in mind some basic definitions.[3,8,20,42]

Competence

Competence or competency can be defined as the cognitive and mental ability to understand problems and make decisions. To some extent, competence is decision specific and is influenced by various environmental, cognitive and affective factors. For instance, a person may be competent to make a particular medical decision, but not necessarily another more complex or different one. Still, individuals having attained their majority (18 years) are legally considered as competent, unless they suffer from a psychological disturbance or intellectual impairments affecting their capacity to act rationally (art. 16 of the Swiss Civil Code).

Minor adolescents or even children can be considered competent, as long as, in a given situation, their health care provider and health care team deem them so[20,43]. According to the Swiss Federal Tribunal, depending on the circumstances, minor as young as 13 year can be deemed competent to consent or refuse a medical intervention. Individuals considered as competent have thus a right for decision making and giving consent; in addition, they also deserve confidentiality and confidential health care. In other words, information is provided to the parents only with the consent of the child. The issue of confidentiality is of particular relevance when it comes to discuss with the adolescent his lifestyles, including intimate matters such as the use of substances and her sexual and reproductive life[29,36]. Any health professional involved in the health care of an adolescent – and this includes access to research and clinical trials – must balance the need for the adolescent to benefit from privacy and confidentiality, and at the same time secure easy communication with the parents/ caregivers[44-47].

Assent and consent: definition[48,49]

Informed consent means approval of the legal representative of the child and/ or approval by a competent child for medical interventions and procedures following appropriate information[50]. According to Art. 23 of the HRA, the adolescent above 14 years can consent alone if the research is associated with minimal risks only. Informed assent means a child's agreement to medical procedures in circumstances where he or she is not legally authorized or lacks sufficient understanding for giving formal consent. Even young children deserve explanations around medical procedure and must be invited to give an opinion, an assent (see art. 6 par. 3 of the 1997 Council of Europe Convention on Human Rights and Biomedicine). Medical procedure should not be imposed to children unless there are important health reasons to proceed; usually, delivering information in warm and respectful climate allows obtaining an assent from the child (e.g. vaccination, blood puncture etc.).

Confidentiality[19,20,36]

Respect of professional secrecy and confidentiality are the cornerstones of the trust patients are entitled to have in their physicians and caregivers. Many studies have confirmed the importance of confidentiality in the care of adolescents[19], and this aspect of the clinical approach of adolescents is considered of utmost importance by young people who have been invited to give their opinion on good medical practice[51,52]. Adolescents considered as competent automatically beneficiate from confidentiality if they ask for, and the health care professional should discuss this issue openly and privately on every occasion, selecting with the young patient which information should or should not be disclosed to parents or caregivers.

Granting adolescents' confidentiality does not mean that the whole content of an encounter should remain secret; young patients should be encouraged to share as much information as possible with their parents/ caregivers. In principle, adolescents who do not possess full competence could still be granted some confidentiality, as they may otherwise not divulge their behavior in specific areas such as sexual life. There are many obstacles for adolescents to receive confidential care

and they should be addressed[19]: some parents may be reluctant and should be convinced of the importance of confidentiality and reassured that their child will be encouraged to share his main concerns. Some adolescents may not trust the health care provider; physical space and lack of privacy, lack of too vague policies, billing the consultation to the parents or insurance are all factors that need to be considered. In some instances, the parents themselves may ask the health care provider to keep some information confidential, a request that may be acceptable, even though keeping such information secret may not benefit the adolescent.

ANNEX 2: Assessing the adolescent's competence

The HRA sets the limit between childhood and adolescence at age 14. However, given the broad range of cognitive and affective development among children, this does not mean, in accordance with the Civil Code, that individuals younger than 14 years are not competent, nor are all individuals older necessarily competent in all situations. The assessment of adolescent competence/ decision-making capacity is a process that should be carefully conducted, often over more than one encounter[8].

The following procedure[8] is derived from the recent publication of the Swiss Academy of Medical Sciences[53] and derived from the seminal work of Grisso and Appelbaum[54,55].

Firstly, it needs to establish an empathetic and trustful relationship with the adolescent: indeed, a safe climate and good communication with clear explanation and feedback (e.g. "informed" consent) improves any child or adolescent's competence[24,25]. It is often useful to include – with the adolescent's consent – other health care providers, relatives, peers, teachers or social and mental health professionals in the appraisal of the adolescent's cognitive and mental health development. It is as well crucial to keep control of coercion and other social forces that influence decision making, such as, for instance, parents who insist on being present on all occasions and exerting pressure on the adolescent in adopting their views.

The assessment of competence is a deliberative stepwise appraisal process, including:

Assess the adolescent's understanding of the different facets of the situation

Information regarding the different clinical facets of the situation or disease or issue should be delivered by the health care provider in a simple, accessible language and should be comprehensive. It is useful to ask the adolescent to interpret what he has understood, including the nature of the condition or decision to make and its various options.

Evaluate the adolescent's reasoning about his/ her present situation, health condition and the therapeutic options

At this stage, the person in charge of the assessment explores the way the young patient applies logic to clarify information, verify facts, justifies change or persistence in opinions and beliefs based on newly acquired or existing information. Questions can be asked such as

- "What would happen if a boy asks you to engage in sexual exchanges?"
- "What makes you think that you can consistently take oral contraception?"
- "Do you imagine that you could require from a boy to use a condom?
- "What would happen if your parents know that you have sex?"

It is also worth to explore how the adolescent feels about his parents' or relative's views and preferences, and how these opinions would affect his behaviour and choice.

Gauge the adolescent's thinking on various options

The young patient is asked to balance the respective risks and benefits of decisions to be made. A specific difficulty of young adolescents is to foresee the long-term consequences of any choice, as the capacity to reason in an abstract and long-term perspective may be hampered due to neurodevelopmental limitations[56]. It is for instance difficult for a 15 years old pregnant teenager to imagine what her life with a baby may look like within two or three years. At this stage, the person in charge of the evaluation must be very careful in accompanying the adolescent in the progression of her understanding of the situation:

- "Can you explain why you think that this option is better than the other one?"
- "Can you compare these two options and list the risks and benefits linked with each and which risks and benefits are, for your future, the most important in making a decision?"

Make sure that the adolescent is able to express a choice, to decide

After this careful, respectful systematic deliberation, the adolescent is asked to express a choice and to justify it in the light of the discussions that have taken place. In some instances, especially among younger adolescents, the evaluation may lead the professional in charge with the feeling that the patient does not understand the potential consequences of the various options and does not display the required level of reasoning to be granted full competence; the health professional should thus convince the adolescent that the information should be shared with the parents. In addition, there are circumstances in which, even if the adolescent understands well all issues and options related to the situation, and has good reasoning capacities, he may feel himself unable to make a decision and consequently not be granted full decision-making capacity.

ANNEX 3: Review of the adolescent's lifestyles: the HEEADSSS approach[29]

For teenagers, a psychosocial review of systems is at least as important as the physical examination. The approach using the HEEADSSS acronym facilitates the assessment of the *adolescents' functioning and lifestyles*.

HEEADSSS stands for **H**ome environment, **E**ducation and employment, **E**ating, peer-related **A**ctivities, **D**rugs, **S**exuality, **S**uicide/ depression, and **S**afety from injury and violence.

Generally, it is preferable to conduct the psychosocial interview when the adolescent is relatively well, under low-stress conditions. Before attempting to review the adolescent's lifestyles, it is important to gather first the information related directly to the more or less urgent complaint or reason for visit. The basic screening interview is designed to be reasonably rapid — otherwise it would not be an efficient tool.

With practice, its content can be covered in around 20 minutes; but in some instances, it can be conducted over several encounters. It is as well crucial to leave the teen adequate time to reflect on the question asked or to tell his or her own story. In addition, the health care provider should not only record the answers, but also provide advices when the adolescent asks for information or discloses a problematic situation or behavior (e.g. depression, unsafe sex, binge drinking episodes, violence etc.).

The use of motivational interviewing is helpful: instead of delivering moralizing messages or just asking the adolescent to change behavior, it is useful to explore *with him or her* how he/ she would himself/ herself address the problem. The discussion should lead to a common, shared view as how to proceed. The extent to which parents should be involved must be debated with the adolescent, who has the right to keep some information confidential if he/ she is considered competent, and as long as his/ her health or life is not heavily menaced (e.g. abuse, suicidal project).

The interest of the HEEADSSS approach is that it starts with questions that are usually enjoyable, about friends, activities, and the last section that is covered is tackling issues that are more sensitive. While asking questions, it is always important to inquire not only on problems, but as well on resources (e.g. connectedness with family & friends, activities the adolescent feels proud about, or that are successful, responsibilities taken in the everyday life, etc.).

Examples of useful questions

The type of questions used must be tailored to the adolescent's age and developmental stage.

Home: Who lives with you? Do you have your own room? What are relationships like at home? To whom are you closest at home?

Education and employment: What do you like mostly while being at school? Tell me about your friends at school? What are your favourite subjects at school? How are your grades? What are your future education, employment plans/ goals?

Eating: What do you like and not like about your body? Have there been any recent changes in your weight? Have you dieted in the last months? How? How often? What do you think would be a healthy diet? How does that compare to your current eating patterns? Do you worry about your weight? How often?

Activities: What are your favourite activities hobby? What do you and your friends do for fun? (with whom, where, and when?); What do you and your family do for fun? (with whom, where, and when)? Do you have a "best" trusted friend around? How do you get along with your mates? How much exercise do you get in an average day or week? How much time do you spend on screen/ internet, and for which purpose?

D*rugs*: Do any of your friends use tobacco, alcohol or other drugs? What about you? If you do smoke, how do you feel about it? Have you ever foreseen to quit? If you drink alcohol, would you allow us to discuss it: how often, on what circumstances? Did you ever get drunk?
Same kind of questions for cannabis or other illegal drugs.

S*exuality*: Have you ever been in a romantic relationship? If you agree, tell me about your sex life; Have any of your relationships ever been sexual relationships? What about you? What does the

term "safer sex" mean to you? Are you interested in boys? Girls? Both? Have you ever been forced or pressured into doing something sexual that you didn't want to do?

S*uicide and depression:* Are you often anxious? What makes you anxious? Do you feel sad or down more than usual? Do you find yourself crying more than usual? Are you "bored“ or tired all the time? Does it seem that you have lost interest in things that you used to really enjoy? Do you find yourself spending less and less time with friends? Are you having trouble getting to sleep? Have you thought a lot about hurting yourself or someone else? Have you ever thought of committing suicide? Alternatively, even attempted?

S*afety*: Have you ever been seriously injured? How? How about anyone else you know? Do you always wear a seatbelt in the car/ use a helmet while biking or using a motorbike or while snowboarding? Have you ever ridden with a driver who was drunk or high? Is there violence around you? Have you ever been physically or sexually abused?

ANNEX 4: References

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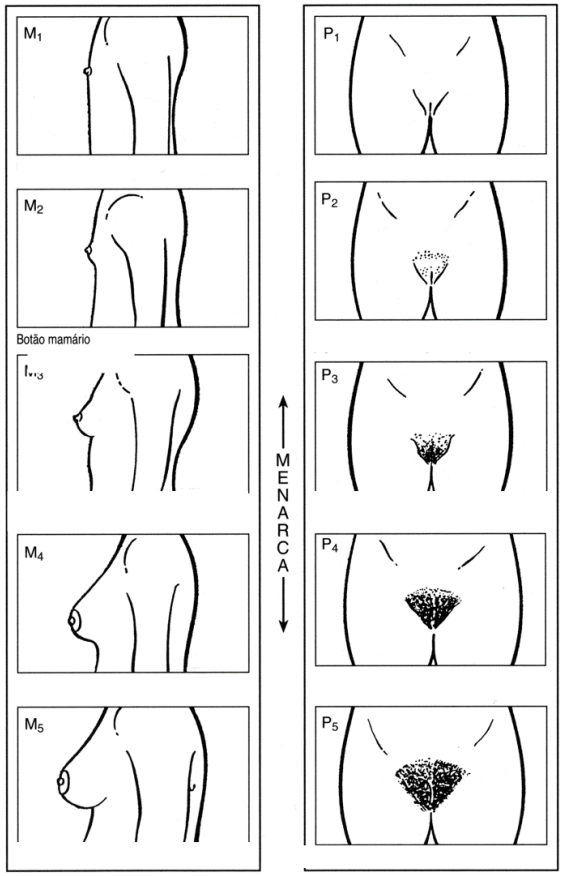
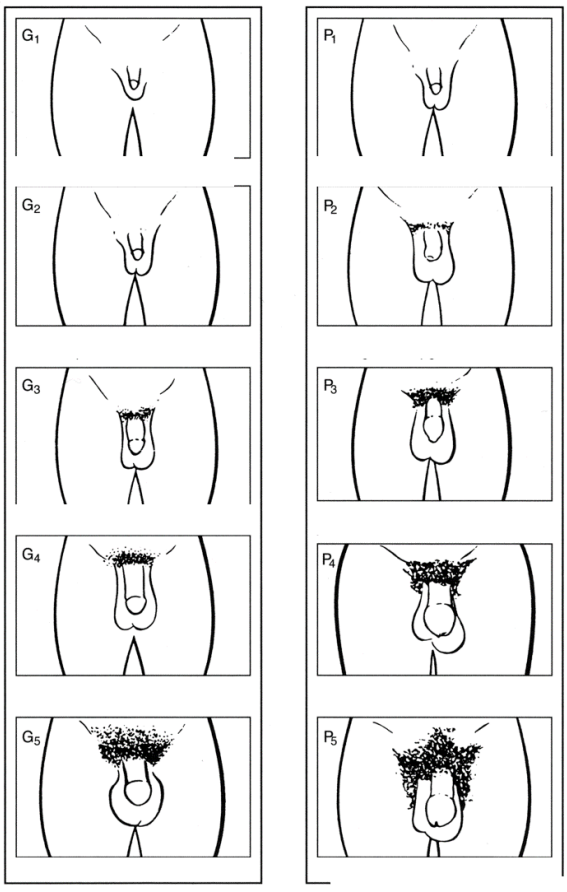
ANNEX 5: Tanner stages (adapted from Tanner J, 1962[11])





ANNEX 6: Algorithm on how to deal with medication prescriptions to adolescents with CBP