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Review Article

Clinical Research Involving Minors in International and Serbian Regulations

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Abstract

Background: Participation in clinical trials can be useful for the health of a person, in who it is conducted, but it does not have to be – it can even be harmful. Therefore, primary motive to accept such risk is humanity and human wish to contribute to the progress of medicine; this is expressed by personal consent. The consent, however, can be an expression of personal humanity, and for this, it is not logical that someone can give consent on behalf of someone else, as it is done by a legally authorized representative on behalf of a minor. Therefore, authors raise 3 questions: What are the reasons to consider representative's consent acceptable? How should a model of regulations look like in order to provide the most complete possible protection to a minor? Is actual regulation of minors' position within international and Serbian law, analyzed here by authors for their specific solutions, acceptable? Representative's consent is acceptable only for therapeutic research, because these can bring benefits to everyone's health, including a minor in which those are conducted – this is an acceptable (secondary) motive of participation in the research. Expression of humanity on other's behalf, typical for non-therapeutic research, is not acceptable; this makes ban of minors' participation in non-therapeutic research more appropriate regulation model. International regulations are not in accordance to results presented in the paper for allowing participation of minors both in therapeutic and non-therapeutic research. Serbian regulation is closer to the most acceptable regulation model.

Keywords: Medical Law, Clinical trials, Minors

Introduction

Informed consent is minimum term to be fulfilled today in order to access clinical research involving human subjects. It is the fact, however, that many are not capable of giving valid consent to participation in clinical research (1, 2). Largest categories of such persons are minors, i.e. children. In general, it is considered that they are not capable of taking care of themselves, or mature reasoning and decisions making regarding personal life issues – for this reason they are not capable of giving consent to participation in clinical trials. This presumption is valid until minor's legal competency that comes with his legal age, independently if a child is capable of reasoning even earlier. Different approach could lead to unacceptable situation where each child individually would be tested for its legal competency. (Before legal age). Everything presented indicates that minors cannot be involved in clinical research since they cannot give fully valid consent to it.

The fact, however, is that clinical trials have to be done exactly in children for medical reasons – research conducted in adults cannot give adequate results (3). Welfare of children population and progress of medicine, hence, demanded involvement of minors in clinical trials. A compromise between two opposite requirements – to have and not to have minor subjects – was made by allow-

ing research involving children if, instead of them, consent is given by an authorized person for that. Such person is legally authorized representative of a minor, i.e. its parent or guardian (4).

Time, however, showed that decisions of legal representatives on behalf of minors are sufficient protection of child's interest when referring to daily life and activities; yet, these are insufficient if refer to consent to clinical research, extending the scope of common issues. Clinical trials are specific because participation in those is not necessary for individual health protection, but it represents primarily expression of humanity and wish of participating person to contribute to the progress of medicine; and then to possibly make benefit for personal health, too. Even if medicine or certain method, effects of which are examined, can be a therapy for subject's illness, by the rule, subject is not aware of the group he will be placed in: the one to take new medicine; or the one that will take placebo (5) or standard therapy for the illness. However, if a subject is healthy, the only reason to take part in a research is pure humanity.

For this reason, described nature of clinical research creates problematic situation where one person accepts research in other person, particularly the one incapable of individual decision-making – a minor. Essence of the problem is the fact that by giving such consent to participation in a research someone expresses *his own humanity* – regardless if he is going to have benefit, or not; or maybe even harm to his own health. However, the question is: how can one person make such decision on other's behalf, particularly minor's? From logical viewpoint, something like that is not even possible; and, it is ethically unacceptable (6). When someone else is making decisions regarding acting of a minor, and decisions are made primarily for the cause of humanity welfare – minor actually is no longer subject, but becomes an object of the research, with potential danger of being misused for general interest (7). Such danger is explicit within the community of low education level; and, worldwide known scandals (8, 9) in connection to clinical trials in children showed that both researchers and sponsors are prone to lack of care for negative consequences of the research if the consent of a legal representative exists (10). Yet, we cannot give up progress of medicine, and obviously, solution to this problem had to be found in prescription of additional terms to be fulfilled in order to include minors into research, besides just having representative's consent (11). Those terms have to be independent of representative's will and their purpose is twofold: to limit participation of children in research only to situations when that is necessary and, to guarantee children's protection from possible misuses (12).

Result of this recognition is the review of concepts for minor subjects' protection, both in international and national levels. Most significant international legal and ethical documents prescribe different number and sorts of additional terms for participation of minors in clinical research; some of them are starting even from a principal ban of their participation in all or some types of research. Primary objective of our paper is to analyze these terms in order to identify up to which level each of the terms individually, as well in combination with other terms from certain international regulation, contribute to protection of minors and what is its direction.

Mentioned tendency to protect minors by prescribing additional terms for participation in research (beside consent of legal representative), did not evade national regulations either. Solutions of Serbian law, which just recently started regulating in details positions of all subject of clinical trials, including minors, can serve as an example of this. It recognized ideas expressed in international regulations, and this is verified by the new Medicines and Medical Products Act, introducing specific system of minors' protection. Although grounded on the same principal idea, that protection is conceptually different from international regulations regarding this issue by the number and type of additional terms. Noticing these differences, we thought that presentation and analysis of Serbian solutions would be interesting for international professional and scientific public. This would lead to the second objective of our paper, which is presentation of the level up to which Serbian regulations contribute to the protection of minors from possible abuses. Comparison of

those is necessity, having in mind differences between international and Serbian solutions.
Finally, based on made analysis, our third objective is to identify a model of regulations that could, in our opinion, provide the most complete possible protection of minors in clinical research; as well to establish which of analyzed regulations is closest to that model.

Minors as Subjects of Clinical Research within International Regulations

The most relevant international regulations stipulating position of minors in clinical research are certainly The Declaration of Helsinki and International Ethical Guidelines for Biomedical Research Involving Human Subjects. Solutions provided in Guideline for Good Clinical Practice will be analyzed in the part dealing with Serbian regulations, since the Medicines and Medical Products Act refers to its implementation making this Guideline an integral part of this legal system.

The Declaration of Helsinki

Declaration of Helsinki (13) (hereinafter: DH) has several versions; however, versions from 2000 and 2008 are relevant for this topic, introducing some additional terms for minors' protection, beside the consent of their legal representatives.
A. Starting point of the *DH version from 2000* is a principal ban of participation of legally incompetent minors in clinical research. The ban is not absolute; therefore, participation is exceptionally allowed with the consent of their legal representative if several additional terms are fulfilled (these are to be commented): 1) research cannot be conducted in legally competent persons (DH, art. 24); 2) consent to participation in research was given also by a minor, if minor is capable of making such decision (DH, art. 25); and 3) research serves to promote health of population represented by the minor(s) (DH, art. 24).
1. Since minors cannot personally give valid consent, logical consequence is to bring their participation in research to minimal necessity. A term that minors cannot participate in research, which can be done in legally competent persons, is a good way to reach this objective.
2. Consent of a minor (14) is also important additional term prescribed by this version of DH. In our opinion, it has two aspects, although these are not clearly separated, as it is the case in DH version from 2008. First aspect of this term is that no one – even child – can be forced to participation in research, if he is explicitly against that. Second aspect is that, even in the case that consent lacks, i.e. minor is neither for nor against the research – he cannot participate in research, too. Participation is acceptable only if minor's consent exist, under the condition that he is capable of formulating relevant decision (15). If he is not capable of this: for his age or other reasons – and there are many minors alike – prescription of this term stays irrelevant, and minor will participate in a research on the basis of legal representative's consent. For this reason, importance of these terms should not be either diminished or overstressed. Even when there is minor's consent, it is not equally valid as adult's one, (16) since minor is not an adult regardless how mature and informed he is. Even when he is capable to understand his situation, that understanding is in accordance to his age and it is not equal to the understanding of an adult, having knowledge and experience gained by ages. If that would not be the case, what would nomination of legally authorized representatives serve to? Therefore, consent of a minor must not be equalized with fully valid consent, although it is useful that 2000 DH foresees this terms.
3. However, term under which a minor can participate in clinical research if it serves to promotion of health of the population represented by a minor – regardless is he going to have personal benefit of the research or not, creates dilemma. This further means clinical trials can be done both in healthy and ill minors suffering of illness to which medicine or method is intended to. Since nature of one research, as therapeutic or non-therapeutic, is determined by criterion can it be a therapy for an illness of *a person in who it is conducted* (subjective criterion) – not by the question can it also be beneficial for someone else (population represented by the minor), this means that DH version form 2000 allows both types of research in minors. If participation in a therapeutic research on the basis of other's

consent cannot be justified minimally by possible usefulness for minor's health, we cannot recognize proper justification of his participation in research leading to promotion of the health of population he belongs to if minor personally has no benefits, and may even suffer damage. It is acceptable if a grown up person makes conscious choice expressed in a form of its consent. But, if legally authorized representative makes such choice on behalf of a minor – that is legally and ethically unacceptable, as elaborated in the introduction of this paper. Therefore, we consider this solution too broad extension of the exception from a ban of minors' participation in research. If all types of research can be conducted in minors, principal ban of their participation loses sense and its protective function. The exception from a ban is so broad questioning the need of its existence at all. We consider useful additional fine-tuning made by this version of DH referring these terms only to the category of legally incompetent minors (DH, art. 24) since it can happen that minor reaches legal competency even before his legal age.

B. *DH version from 2008* changes terms under which minors can participate in clinical research, regulating their position together with other categories of persons not being capable to give consent to clinical research on their personal behalf.

1. While DH version from 2000 sets principal ban to participation of *all* minors in *both* clinical trials (exceptionally, if above mentioned terms are fulfilled), 2008 version bans participation of minors only in research where *no direct benefit for minor is expected*, i.e. non-therapeutic research. *Argumentum a contrario*, each minor can participate in therapeutic research with his consent and consent of his legally authorized representative (DH, art. 27), with no additional terms fulfilled. It means that 2008 DH version widened a circle of minors who can become subjects: principal ban of participation in all researches from 2000 is wider than principal ban of minors' participation in non-therapeutic researches from 2008. While according to the version of DH from 2000 participation of a minor both in therapeutic and non-therapeutic research was exceptional under above mentioned conditions, from 2008 minor can participate therapeutic research whenever he has benefits of that – even if the research could be conducted in legally competent persons, since this is not a terms required by the DH version of 2008. On the basis of presented we have to conclude that minors' protection within the DH version from 2008 is on a low level and should be supplemented at least by the requirement that it is not possible to conduct research in legally competent persons.

2. However, DH version form 2008 allows also exceptions from the principal ban to conduct *non-therapeutic research* in minors, expanding further circle of minors who can become subjects, under following terms: 1) research cannot be performed with legally competent persons (DH, art. 27); 2) research serves to promotion of health of the population minor is representing (DH, art. 27); and 3) research entails only minimal risk and minimal burden (DH, art. 27). Therefore, these are the same terms, which *each minor* had to fulfill to become a subject by the DH version of 2000, adding just one new term – minimal risk of the research for minor. Addition of this term is considered adequate, because it takes into consideration the fact that minors differ from adults not only by lower reasoning and decision-making capacity, but also by incomplete physical development. Possible negative consequences of non-therapeutic research will certainly reflect more drastically upon the health of developing person then upon the health of an adult, and for this, it is of immense importance to have minimum risk when research subjects are healthy children (17).

Although terms of minors' participation in clinical research in the DH version from 2008 are formulated in a way which at the fist glance may look like ban of participation in non-therapeutic research that provides better protection than DH version from 2000 – essentially, as it can be seen, this is not a case. According to the DH version from 2008 each minor can participate research if he has direct benefit of it (no additional terms); but, also if he will not have direct benefit, but the research may contribute to improvement of the health of population a minor subject belongs to (on this occasion – with the fulfillment of above presented additional terms). Participation of mi-

nor is possible both in therapeutic and non-therapeutic research under different terms. Since clinical trials are suppose to be conducted in minors, and consent to that is given by legal authorized representative – we are not sure that mentioned determination of the DH version from 2008 is correct for already mentioned reasons, particularly non-therapeutic research related ones.

3. Such solution within the DH version from 2008 is more acceptable only for the fact that it foresees not only necessity of his consent to participate in clinical trials, but also that his dissent from participation in the research has to be respected, if he is capable of making such decision (DH, art. 28). This pays respect of each individual's autonomy, even when that individual is minor (18). Although we think that even solution from DH version from 2000 should be understood in presented sense, we consider useful that DH version from 2008 formulates mentioned terms more precisely and as such removes possible dilemmas. Hence, all reservations we have made regarding importance of this terms while commenting the solution from the DH version of 2000 are valid for the version from 2008.

International Ethical Guidelines for Biomedical Research Involving Human Subjects

International Ethical Guidelines for Biomedical Research Involving Human Subjects (19) (hereinafter: Guide) put children explicitly into vulnerable subjects (20) (21); consequently, two groups of terms have to be fulfilled for their participation in research: those intended to minors' protection foreseen by the Guideline 14; and terms that have to be fulfilled for participation of any vulnerable subject in clinical trials as foreseen by the Guideline 13. These terms do not differ much; except that Guideline 13 foresees two terms more than Guideline 14, as it will be elaborated hereinafter.

1. Terms within the Guideline 14 referring only to minors (beside legally authorized representative's consent) are: 1) research cannot be equally well be carried out with adults; 2) objective of the research is to reach knowledge relevant for health needs of children; 3) a child agreed to participate in the study, if capable of making such decision; and 4) opposing of a child to participation in or continuation of the research, when it is capable of forming its opinion of the research, must be respected. It is interesting that Guide requires respect of both child's refusal to participate in the research, and refusal with a character of child's withdraw of already initiated research to which it has already agreed. In the comment of the Guideline 14, the Guide contains useful interpretation of the last term according to which action against the will of a child can be explicitly undertaken if it is about therapeutic research; if a child needs treatment which is not available out of research context; and, if there is no acceptable alternative therapy for child's illness. In this case, representative's consent is sufficient, and if a child is close to legal age (22), action requires consent of an ethical committee. By this, the Guide sets balance between minor's health protection and respect of the right of each person to self-determination about its own body.

2. Beside mentioned terms of the Guideline 14 creating specific protection of a minor, as it is already said, terms from the Guideline 13 regulating protection of all vulnerable subjects have to be fulfilled. For minors this means fulfillment of two more conditions and these are: 1) participants in the research, but also other members of the vulnerable group, shall be provided with the reasonable availability of the tested method afterwards; and 2) expected risk of the non-therapeutic testing is minimal with an option of its slight increase upon the approval of ethical committee. We consider reasonable availability of tested method one important term, because it provides benefit for the health of minor also after finished research; this additionally „covers", and justifies the fact that consent to their participation in research is given by other person.

3. As it can be seen, unlike DH, the Guide does not forbid participation of minors in both types of researches. Minor can participate in any research serving to satisfaction of the health need of children, regardless personal interest of the minor or not, i.e. regardless is the research therapeutic or not. Besides, almost the same terms have to be fulfilled as those foreseen by the DH version form

2008 for participation of minors *in non-therapeutic* research. It means that the Guide provides greater protection than DH version from 2008 narrowing the possibility of their participation in research: by the Guide *all* minors have to fulfill additional terms for participation *in both researches*, not only non-therapeutic, as in the DH version from 2008.
Speaking of relation between the Guide and the DH version from 2000, contrast of the starting points is just an illusion; although the Guide starts form positions opposite to this version of DH (participation of minors in research is allowed, not forbidden). According to the Guide, participation of minors is possible in both researches, but with the fulfillment of mentioned terms; by the 2000 DH version it is also possible for both researches, but as an exception to the rule on ban of participation – under almost the same terms. From the viewpoint of minors' protection – both documents cause almost the same effect.
The difference between both versions of DH and the Guide is that Guide sets necessity for a minor to have tested method available also latter on, and that is particularly important in non-developed countries.

B. Minors as Subjects in Clinical Research within Serbian Law

Position of minors in clinical research of medicines and medical products in Serbia is regulated by the Medicines and Medical Products Act (23) from 2010, amended in 2012 (hereinafter: the Act). The Act is not enforceable for performance of other medical experiments in minors[1]; therefore, this will not be the subject of this paper. Since the Act in its article 59 refers to implementation of Guideline for Good Clinical Practice (24) (hereinafter: GCP) in conducting clinical research, content of this GCP is also an integral part of the legal system of Serbia.[2] Solutions of both regulations will be presented and analyzed in the conti-nuation of the paper, as well as issue of co-relation when these regulate position of minors in different manner.

Position of Minor According to the Medicines and Medical Products Act Minors to whom the Act refers

Referent group of subjects within the Act is defined by ages. These are persons under 18, i.e. minors, since legal age in Serbia is reached with 18. By the rule, these persons have no legal or reasoning competency, although it does not have to be the case. Some minors can reach legal competency by the decision of the court even before reaching legal age (but not under 16) for reasons defined by the law (art. 11 and 23 of the Family Act) (25). This causes dilemma: do provisions of the Act refer only to legally incompetent persons or to all minors? In our opinion, first option is more acceptable; however, more preciseness in the Act would do good as it is the case with international regulations in this area.
Not all minors are enjoying the same protection, in the context of clinical research. The Act differently regulates position of two categories. The first one is composed of healthy minors (art. 63 par. 1 points 1 and 3); and, the other group are those suffering of illness or being in condition to which tested medicines are intended to (art. 63 par. 2, and art. 64).
There is a group of minors whose position is not regulated by the Act. These are minors not suffering of the illness medicine is intended to, but are not healthy either for suffering of other illnesses. Although the Act would remove possible dilemmas by their classification in one of the categories position of which is regulated – in our opinion, even without such classification there are grounds to conclude that in this context they belong to the group of healthy minors. Namely, their illness is «inadequate» to join them to the group of minors having illness to which medicine is intended; there-

[1]Terms to conduct *other medical experiments* in minors and other subjects prescribed by the Health Care Act – art. 38 („Official Gazette of the Republic of Serbia" 107/05, 72/09, 88/10, 99/10, 57/11).

[2] Guideline for Good Clinical Practice was included into the legal system of Serbia in 2008 under the title "Guideline for Good Clinical Practice in Clinical Research" ("Official Gazette of the Republic of Serbia" 28/08).

fore, they should enjoy the position prescribed for the category of healthy minors.

Healthy Minors as Clinical Research Subjects

In Serbia, healthy minors (as well as those suffering from so-called «inadequate» illnesses) cannot participate in clinical research of medicines (art. 63 par. 1 point 1 of the Act). It means that non-therapeutic researches over minors are forbidden. The Act, however, makes one exception from the rule, allowing this option also for healthy minors under fulfillment of two terms: 1) it has to be in their interest; and, 2) their legally authorized representative agreed to that (art. 63 par. 3).

Mentioned solution of the Act deviates from the one represented by analyzed international regulations, since possibility of non-therapeutic research in children is set significantly narrower. Firstly, nature of terms under which it is possible to conduct such researches in Serbia is as such that in practice terms can rarely be fulfilled. Namely, it is difficult to find a situation where non-therapeutic research of the medicine is in the interest of a healthy child in who research is conducted. Terms of the international documents, hence, usually can be fulfilled (ex. research cannot be conducted in legally competent persons and serves to promotion of the health of minors' population). Secondly, even when happens that non-therapeutic research is in the interest of a healthy minor, *existence of his interest makes this research "closer" to the therapeutic one* – and, this is not the case with international regulations. There, possibility of minors' participation in non-therapeutic research is wider: a minor does not to have to have direct benefit from the research and it does not have to be in his interest. Benefit for the population he belongs to is sufficient.

We consider this solution of Serbian law more adequate then the international one. Because, it narrows option of minors' participation in research, he is not going to have personal benefit from, and decision about that – as a human act for the purpose of medicine progress – is made by legally authorized representative. Something similar is not logical and therefore, is not acceptable – as already discussed. We are of the opinion that even consent of the minor to participate non-therapeutic research, as it is the requirement of most of the international regulations, is not sufficient solution for this situation equal to the justification given to it by the possible benefit to minor's health. Therefore, therapeutic researches seem only acceptable solution for minors. In our opinion, ethical boards in Serbia should carefully identify the interest of each minor subject when approving non-therapeutic research, not to turn this exception into the rule.

Ill Minors as Clinical Research Subjects

Minors suffering of illnesses or being in state for which tested medicine is intended to, can be subjects by the Act if that is necessary and with special precaution measures (art. 63 par. 2), as well with additional 6 terms fulfilled (art. 64 and 65).

1. First term, as in all international and national regulations, requires consent for that given by minor's legally authorized representative (art. 64 par. 2 point 1). Its fulfillment guarantees minimum protection for a minor who is not capable of formulating legally relevant will, as legally incompetent person usually also incapable of reasoning.

2. Second term is that representative's consent represents presumed wish of the minor (art. 64 par. 2 point 1). This primarily means that representative, beside assessment: is the research objectively in interest of the minor, has to take into account also one subjective moment – minor's wishes, in accordance to the position that each man has to be treated as subject of the research. Since representative has to take care of presumed wishes of the minor – and that is not expressed wish but the one existence of which is recognized by the representative knowing positions of the minor (if minor is capable of forming positions) – we think that representative has to take even more care of minor's expressed wish. Although the Act is not foreseeing this explicitly, it is an opinion of ours that such formulation means that minor cannot be forced to participate in research he is opposing to, because that obviously is not in accordance to his wishes – presumed or expressed (26). Regulations of certain countries (27), as well some of analyzed international regulations explicitly foresee this, regu-

lating also actions in the case of minor's disagreement with representative's position to participate in the research. Serbian law, however, does not explicitly foresee solution for such situation.

Since opposite situation is also possible: minor expresses a wish to participate in the research and legally authorized representative is opposing, the question is raised: whose position will be a primary one? Formulation of the legal text we are commenting as such is giving grounds to conclude that representative's position has equal importance as wishes of minors, i.e. minor could not participate in the research either he personally does not want that and legal representative considers it necessary; or minor wants to participate, but legal representative disagrees. We are of the opinion that subject provision cannot be understood differently than as follows: representative's consent actually „absorbs"also the wish of a minor – presumed if it was not expressed by him, and particularly expressed one. Anyhow, it would be useful to amend mentioned provision of the Act and make it more precise, as done by the Guide within its above-elaborated Guideline 14.

3. Third term is that minor has to be informed about the course of research, risks and benefits it bears to his health, equally as his legally authorized representative; this has to be done in a comprehensive way by a person having experience in work with minors (art. 64 par. 2 point 2). We consider this term properly set since it provides not only respect of minor's personality respect – a minor also has to know what is going to happen with him, but it enables minor to formulate his position and wish pertaining to participation in the research based on presented facts (28). Representative has to take all this in account when giving consent. Minor's awareness of information provided directly influences also representative's de-cision. When provided by a professional, information guarantees quality, not only formality, and opti-on for a minor to formulate his position with essential understanding of provided information.

Although both international documents and Serbian law require for *all* subjects and their possible representatives to be previously informed in order to give fully valid consent to participate in research, we think it is good that the Act specifically prescribes this term and prescribes it within provisions regulating position of minors. By this, it underlines its importance; removes dilemmas is it necessary to inform also minor, beside the legal representative; and, gives more precise qualifications a person providing information has to have – this can be a researcher, but not necessarily. Serbian regulation of this term is more complete than the international one.

4. Fourth term set by the Act is that given consent to participation in research can be withdrawn at any moment, with no consequences for the minor (art. 64 par. points 1). Logically, this can be done by a consent-giving person – legal representative; it is interesting, however, that the Act gives such option also to a minor capable of forming opinion and assessing information provided. It is not a minor who actually *withdraws his consent*, but his representative is, as the Act is not demanding consent from a minor. He can withdraw the consent at any moment, i.e. abandon the clinical research (art. 65); this is one more argument supporting the position that minor's wish has almost the same „weight" as opinion of the representative, and that assent to the research actually means consent of all persons affected. Possibility to abandon research, with no limitations pertaining to background reason or moment of time when that can be done, maximally protects minor's interests.

By the international law, right to withdraw (research) belongs to each person in the role of subject and it can be concluded that it is valid in the case of a minor, too. But we consider useful that only the Guide and the Serbian Law foresee this right explicitly and within provisions regulating position of minors within research.

5. Next term is that consent was given with no inducement to participate in research by offering or providing material or other benefit (art. 64 par. 2 point 3) – this is considered important, since Serbia is relatively highly positioned globally on the list of corrupted states[3]. Setting of this term is im-

[3]By Transparency International corruption perception index for 2009, Serbia was at 83 position in the world with index 3, 5. See:

portant also for the fact that Serbia is a poor country, with low population' education level; altogether this can result in representative's consent to participation of a child in research more for offered benefit and less for his assessment that it is in the interest of a child. Unlike Serbian law, analyzed international regulations[4] categorize this term among general ones related to the provision of consent from each subject or subject's representative, valid consequently for minors, too.

6. Last two terms refer to acting of the Ethical Board (29) when minors appear as potential subjects. The Act firstly prescribes a term according to which minor can become subject if Ethical Board gave positive assessment that the research in him will give direct benefit for *certain group of patients*; as well that such research is relevant for the assessment of data obtained by clinical research in persons capable of giving their consent independently (art. 64 par. 2 point 4). Fulfillment of this term is important to assess is conducting of the research justified and should it be approved. However, we cannot see the connection between a direct benefit for a certain group of patients that research gives and special protection of concrete ill minor that should be the priority. This term is even partly opposite to art. 60 of the Act, contained also in some international documents, prescribing that rights, safety and interest of a subject have to have priority over society and science. In mentioned situation, possibility of a minor's participation is determined by an answer to the question: is the research *in function of the interest of the certain group of patients*, and this is even treated as a term and form of *minor's* special protection. Assessment that some group of patients will have benefit from minors participation does not mean special protection of the minor himself; therefore, this term is not in accordance to the title of the article prescribing it („Protection of minor subjects in conducting of clinical research") and it does not belong there since it is not performing protective function to which it is intended. Existence of this article, however, is not quite irrelevant if we take that its point is that research cannot be done if created as useful only for concrete ill subject minors, but they require wider relevance. It is obvious that this requirement was not skillfully formulated and it does not belong to terms regulating participation of minors in research.

7. Next term is positive decision on research conducting given by Ethical Board but based on the opinion of a physician-pediatrician, particularly focusing to clinical, ethical and psychosocial problems in implementation of clinical medicine testing (art. 64 par. 2 point 5). Requirement for Ethical Board to make decision on minor's participation in therapeutic testing based on the opinion of physician-pediatrician represents important form of minor's special protection. This term is not foreseen by international regulations what makes it positive specificity of the Serbian law.

Second requirement pertaining to the obligation of the Ethical Board to take care of clinical, ethical and psychosocial problems that can appear in research conducting when making decision about it cannot be considered specific minor's protection. We think that this has to be taken into account when decision is made about any research; therefore, it more belongs to general terms of research conducting and provisions related to competencies of ethical boards, then the part on minors' protection.

8. On the basis of presented it can be concluded that common issue for international and Serbian regulations is that they allow therapeutic research to be done in minors, but after additional terms to those valid for adults are fulfilled. Except representative's and minor's consent (if minor is capable of giving it) as the term set by all analyzed regulations, number and type of the rest of terms differ. While DH version from 2008 takes this as the only additional term for participation of minors in research, demands of the Guide are also: research cannot be equally successfully conducted in adults, and testing results have to be available to participants. Serbian regulations do not require fulfillment of these, in our opinion important terms of

http://www.infoplease.com/world/statistics/most-corrupt-countries-2009.html (access: March 2013)

[4] Guideline 7 of the Guide contains particularly detailed regulation of this issue contains under the title „Inducement to participate in research".

minors' protection; therefore, we consider that is the direction for their amendment, including the term of minimal risk of the research in minor, as required by international regulations only for non-therapeutic research. On the other side, Serbian law foresees necessity to fulfill some other important terms, as for example, the opinion of physician-pediatrician has to be provided before a research in minors.

Position of Minors According to the Guideline for Good Clinical Practice

1. Unlike the Act, according to GCP (point 4.8.12.), each minor, regardless suffering of illness medicine is intended to or being healthy, can be participant in a clinical research. Both therapeutic and non-therapeutic research are allowed in each minor if consent for that is given by his legally authorized representative, but also by the minor himself – if capable of doing so. According to the GCP, as by the Act, before giving consent he has to be informed about the research up to the degree he is able to understand provided information, as well as his representative. All subjects, even minor ones (and their representatives), can withdraw given consent at any moment; and, the consent must not be obtained by offering of any benefit (p. 4.8.3.). It means that all minors can participate in clinical research, although they are not all capable of giving personal consent – some based on representative's consent and some based on their personal and representative's consent. GCP does not regulate situation where positions of legally authorized representative and minor do not match.

Hence, when it comes to non-therapeutic research, recommendation of GCP is that only persons capable of giving consent personally and signing it should participate in these types of research (p. 4.8.13.). Testing should be done in minors (and other persons not being able to personally give consent) if they suffer from the illness or being in conditions to which tested medicine is intended; even then minors should be carefully monitored and excluded from the research if there are no doubts about their inconvenience caused by testing – that is also the recommendation of following 4.8.14. Point 2 of the GCP. This means that non-therapeutic researches including minors, however, are treated as an extraordinary situation.

Beside mentioned recommendations, GCP allows participation of minors in non-therapeutic research (p. 4.8.14.), but with fulfillment of additional terms that are not obligatory for therapeutic research: 1) research cannot be conducted in person capable of giving personal consent; 2) predictable risks, as well negative impact to minor's welfare are low; 3) Ethical Board gave favorable opinion of their involvement in the research; and 4) research is not forbidden by the law.

2. Presented leads to the conclusion that regulation of the position of minor research subjects in GCP is mostly similar to the regulations within the DH 2008 version: each minor can participate in each clinical research, both therapeutic and non-therapeutic; however, for the second ones, additional terms have to be fulfilled beside consent of both minor and its legal representative. These terms are almost the same as those foreseen by the DH version from 2008. A significant difference is in the requirement of GCP – research must not be forbidden by regulations of the state where it takes place.

3. Provisions of GCP, however, differ from provisions within the Act on Medicines and Medical Products, and since both are an integral part of Serbian legal system, a question of their mutual relation is raised.

If it is about *therapeutic researches* involving minors: these are allowed by both the Act and GCP, but more terms for these are set in the Act. Since GCP is supplement and elaboration of solutions from the Act, therapeutic research including minors shall be conducted with the cumulative fulfillment of all terms prescribed by both regulations.

The difference in provisions between the Act and GCP is bigger regarding *non-therapeutic researches*. While the Act in principle bans those, with an exception of the situation when non-therapeutic researches are in the interests of healthy minor, GCP allows non-therapeutic research if additional terms for these are also fulfilled. Nature of these terms, however, suggests they will often be ful-

filled. This can lead to a situation where something forbidden by the Act is allowed by GCP. Solution of this situation may be found in the last term of GCP regarding conducting of non-therapeutic researches by which research is not possible *if forbidden by the law*. Although the intention of this provision is to ban research as such, it is an opinion of ours that the whole research can be considered forbidden if its conducting in certain subject is forbidden – as it is the case in Serbia with researches in healthy minors. Therefore, we think discrepancy between provisions of the Act and GCP is settled to the benefit of the Act, which sets principal ban of researches in healthy minors.

Conclusion

Since general interest requires clinical researches also in children, based on everything presented we will try to conceptualize a regulation model, which would guarantee, in our opinion, most complete protection of children from possible misuses.

Base and starting point of this protection certainly has to be consent of minor's legally authorized representative, which, however, must not be the only term for its participation in the research. An answer to the question: why it is the case, comes from the nature of clinical research and subject's motivation to participate in it. While the only motive of the subject to participate in *non-therapeutic* research is its humanity, motive for the consent to *therapeutic* research is twofold: humanity, but also hope that research will lead to subject's healing. Since only individual humanity can be a reflection of the consent to clinical research, such decision on other's behalf it not possible to make – therefore, representative's consent is not sufficient for minor's participation.

Therefore, the most appropriate regulation model has to be grounded on non-exceptional ban of minors' participation in non-therapeutic research. Similar solution is recommended also by the Ethics Working Group of the Confederation of European Specialists in Pediatrics (30). But, *participation of minors in therapeutic research also must not be based only on the consent of legally authorized representative.* Reason for that is in the fact that expected benefit for the health of a minor justifying allowed minor's participation in such research does not necessarily has to be result of the research. For this reason, some other, additional terms have to be fulfilled, beside representative's consent, in order to provide protection of minor's health. In our opinion, these should be at least following 4 terms.

First term is verification that research cannot be done in adult, legally competent person. This term secures participation of children in research only when necessary.

If a research has to be conducted in children, next term is to carry minimum predictable risks and negative effects to minors' health, because it is unacceptable to expose ill children to risky non-tested treatments from which they can suffer more serious damages instead of already approved therapy.

Next term has to be obtained positive opinion of a pediatrician on the suitability of the ill child to be research participant. In our opinion, this should be a physician already treating the child. This is possibly even the most important form of protection for the child. Consent of the child to participate in a research, if it is capable of forming such position due to his maturity, should be the next term. Child's consent has to be consequence of information provided to him by a person experienced in work with children of his age. We have left this term as the final one because we thought its relevance should not be oversized. Child's refusal to participate the research should have more relevance than child's consent. Disrespect of refusal would mean forced participation of a child, and that unacceptable. On the other hand, child's consent does not have the same strength as consent of an adult; and minor is not an adult.

The term of reasonable availability of results to research participants we consider desirable, but not necessary.

After we have presented suggestion of the most acceptable model of minor's protection, we would conclude that concept of Serbian law based on principal ban of non-therapeutic research in minors is closest to this model. Analyzed interna-

tional regulations are grounded on principle of allowed both therapeutic and non-therapeutic researches in minors, or similar or even equal terms, infringing the principle that subject's welfare has to be above the interest of society and science. This principle is certainly not respected with non-therapeutic research.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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