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Terms of clinical research consent's validity

Uslovi za punovažnost pristanka na klinička ispitivanja

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Introduction

Clinical researches of new medicaments and medical products on animals and humans are preceding and unavoidable stage before its application. While from the legal standpoint animals are objects and, therefore, can be considered as things within a clinical research, a human becomes legal subject in all areas of his actions by the moment of birth, including clinical research performed over it. Although underlining this fact might be considered superfluous, World War II and Nazi camps should not be forgotten [1] for the cruelest medical experiments performed against humans without their consent, treating them as mere objects. Modern history also gives examples of humans' abuse for these purposes [2], due to which commenced legal stipulation of the position of people participating in clinical research, as well as terms under which this is possible. Although general agreement exists that clinical trials cannot be denied regardless the risks they carry against health of its subjects – there is also a general agreement that we have to renounce trials performed disrespecting subjectivity of those who are subjects of it [3].

To respect subjectivity of persons who are the subjects of clinical research means their consent to submit themselves to research [4]. We can, thus, name consent the border line between a human as a subject and an object of the research. Realizing its importance, experts from the area of medicine, ethics and law defined terms for consent to be fulfilled in order to consider it valid [5]. Therefore, many international and national regulations set rules for that. However, those regulations are often not harmonized, and the same issue is stipulated in different manners and no clear guidelines are given to researchers how to act, although they are often personally tasked to get subjects' consent. Researchers also do not have all the rules in one document which if to be applied guarantees getting valid subjects' consent and protection of their subjectivity, but also protection from potential researcher's accountability for getting invalid consent.

Having all the mentioned in mind, we collected and analyzed terms that have to be fulfilled in order to consider validity of subject's consent for medical research, starting from solutions in the Serbian law, as well as in international legal and ethics-related documents. In that spirit, we stress as the most important that consent originates from legally competent person or legally authorized representative of legally incompetent person or person incapable of giving consent; it has to be given voluntarily, i.e. must not have shortcomings in a form of the so-called "defects of will"; and must have the attribute of an informed one. A precise definition of terms for validity of research subject's consent in Serbia, however, is not an easy task both for a lawyer and for a physician, since regulations regarding this are given in several legal texts: the Health Care Act [6], the Medicines and Medical Devices Act [7], the Family Act [8], the Obligations Act [9], as well as in Guidelines for Good Practice in Clinical Research (Guidelines) [10], and in international conventions ratified by Serbia. The number of these regulations that have to be kept in mind, can be a problem for a researcher, therefore, objective of our paper was to facilitate researchers in their focus on medical aspects by analysis of legal aspects of consent to clinical researches. Finally, in the last part of the paper, we will indicate also the form of possible accountability of researchers for performing clinical trials with no valid subjects' consent.

Legal competence of the subject

Minimal quality of each consent marking it as "absolutely essential", the term for any experiment against humans, ever since the Nuremberg Code [11] till today, is to be voluntary. Since consent to participate in clinical research in legal terms represents expression of will, it can be considered

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voluntary only if it originates from a person that can formulate legally relevant will, i.e. legally competent person. Legal competency of a person by the rule means its reasoning capability [12–14]. Legally competent (research) subject can be temporarily incapable of reasoning (under influence of alcohol, drugs, etc.), but that is obvious for a researcher and therefore consent getting in such shape can be avoided. However, in some states reasoning capability in this context is considered more relevant than legal competency [15]; thus, it is taken that each person capable of reasoning can give valid consent. Although this position is not illogical, we think that a subject in Serbia has to be legally competent in order to give valid consent (all until corresponding regulations do not foresee differently), and that a researcher has to take care also of the existence of subjects' capability to reason and to inform a competent authority if it recognizes that this lacks temporarily or permanently for some reason.

1. Legal competency is gained by the majority that in different states means different ages – most often 18 (also relevant for Serbia), 21 or 25, with the tendency to lower this limit. Exclusively, legal competency can be acquired even earlier by the so-called public emancipation, if that is acknowledged to a certain person by the decision of competent authority (unlike private emancipation, given by parents, that is not possible in Serbia). Reasons to acknowledge legal competency before the majority are different, and in Serbia that is possible for persons married by the permission of the court or who became parents independently of being married even if in the age of 16 but mature, capable to independently take care of him(her)self and personal rights and interests (Article 11 and 23 of the Family Act). These persons keep their legal competency even if the marriage is terminated. For a researcher it is relevant to obtain legally relevant statement of will from every legally competent person, and therefore also valid consent – independently of how and when the subject gained that legal competency.

Legally incompetent minor, therefore, cannot give duly valid consent to participate in clinical researches, but most of international and national regulations provide an option for that – to be done by their legal representatives instead (or beside them). Serbian Medicines and Medical Devices Act (Article 63) went, however, one step further, prescribing the ban of participation in clinical researches for this category of persons. Exclusively, they can be research subjects with the consent of their legally authorized representatives only if suffering of illness or are in the stages of illness for which clinically tested medicine is intended to (if that is necessary and under special precautions measures); or they are healthy and their participation in the medical experiment is for their interest. Thus, no difference is made between therapeutic and non-therapeutic experiments, as it is done in some European countries [16].

This Serbian regulation, however, does not deal with legally competent or legally incompetent persons, but introduces this ban for persons under 18. Since some minors, as mentioned, can gain legal competency even before the majority, the question is raised are they capable of giving duly valid consent? We could solve this dilemma starting with the question: is getting age of 18 in life legally or medically relevant? The answer is simple: turning 18 is legally relevant because it leads to legal ages and legal competency. From the medical viewpoint, this fact is not relevant, since it happens that exact participation of these persons in research is needed. It is also the fact that different states link legal competency to different ages; and from this viewpoint it is clear that a Serbian legislator obviously had in mind legal competency – not ages as such – when prescribing ban of participation in research for persons under 18. The law linked ban to ages most probably because the number of situations when minors are also legally competent is negligible small. Therefore, it was more correct to use the term "legal competency" in this law instead of indicating ages, as done in for ex. the Health Protection Act (Article 38) regulating validity of the consent to medical measure. We consider that persons under 18 in Serbia can also give duly valid consent to clinical researches if they are legally competent (legal competence means also capability of reasoning, since it is granted by the court. In any case, in order to remove any possible perplexities, the Medicines and Medical Devices Act could also foresee, as by the model of Serbian Organs Transplantation Act [17], that person giving its consent to participate in clinical trails – exactly as person giving consent to donate its organs [18] has to be both legally competent and capable of reasoning, as well of legal age (Article 42 etc.). Although, by the general rule, mentioned characteristics of one person exit's simultaneously (an adult is both legally competent and capable of reasoning) such regulation would solve dilemmas in explicit situations where that is not the case.

The question that is raised in relation to legally authorized representative in this context is: should we make a difference there between persons under 14 and those between 14 and 18 (junior and senior minors), as by general rules of Serbian law contained in the Family Act or not? According to these rules, the difference between these categories of persons are that senior minors are limited in their legal competency and they can independently give duly valid statements of will, and thus also consents to researches – if obtain previous or latter consent of the legally authorized representative. Junior minors cannot independently give statements of will (except for jobs of smaller significance or jobs not creating particular obligations for them), but representatives give consent on their behalf (Articles 64, 72, etc. of the Family Act) – something researcher has to take care of. It is an opinion of ours that these general rules should be valid also in the context of consents to participate clinical researches, because consent is a statement of will as any other.

2. Researchers have to have in mind that not all adults are legally competent. Some of them – incapable of reasoning or to take care of themselves and protection of their rights and interests, or they directly endanger their or others interests (ill persons, person with difficulties in psychophysical development, etc. - Articles 146–147 of the Family Act), can be denied of legal competency totally or partly by the decision of competent authority. These persons also cannot give duly valid consent to clinical research; therefore, a researcher has to inquire do they also have legal competency,

except of being over 18, as requested by the legislator. It would be good to foresee this by regulations, i.e. have this question as a mandatory content of the interview between researcher and potential subject. This is also an argument supporting the position that existence of legal competency is important both for persons over 18 – not only ages. Even if subjects are adults lacking legal competency, their consent given in the so-called *lucida intervalla* of a mental illness, cannot be considered duly valid for legal certainty reasons – until legal competency is acknowledged back by the decision of a competent authority.

According to the majority of international and national regulations, as well as according to the Serbian Medicines and Medical Devices Act (Article 61) both legally incompetent and adults with limited legal competency can be involved in the research, if consent is given by their legally authorized representatives (also including some other terms fulfilled, but not elaborated here since those are not the topic of our paper). By this Act, however, a consent of a legal representative is necessary also for legally competent adults incapable of giving the consent (ex. state of unconsciousness) – under the condition they did not reject to give consent to participate the study before their incompetence begun (Article 66). Mentioned expansion of the group of adults for who consent is given by legal representatives is acceptable, because those persons at the given moment are obviously incapable to give valid consent although formally legal competence exists; however, the question is raised: Who are their legally authorized representatives [19]? Since the mentioned Act does not define this, a representative of the legally competent person in such state cannot be nominated by the researcher – the only solution left is that this should be done by the guardianship body. But, it can perform such action just after it denies legal competency of such person by the procedure prescribed by the Family Act, and this requires time. On the other hand, the question is will then the consent of (newly) appointed guardian be of any relevance, particularly if subject incompetence was of temporary character and clinical research referred exactly to the state in which subject person was (ex. state of unconsciousness). Therefore, we consider that this Act should foresee options of analogue enforcement of regulations from the Health Care Act (Article 34) by which such consent to a medical measure can be substituted by the conclusion of a consilium; however, this option, to our opinion, should be limited only to experiments having therapeutic character.

3. As the following question we should consider: on the basis of which criteria can legally authorized representatives give consent on behalf of the subject they represent [20, 21]? Do they give consent starting from their personal position; i.e. would they give it if they were in the position of the represented person; or they should give it independently of their beliefs (religious and others), but taking care exclusively of interests of the represented person [22]? The second approach is obviously more correct, but what guarantees we may have that representative will act that way? Therefore, it is our opinion that each legally authorized representative or at least guardian as legal representative should obtain consent of the guardianship body, before it gives consent to participation of the represented person in a medical experiment, particularly if it is of nontherapeutic character. In the Family Act of Serbia there already is a provision (Article 137) by which a guardian can give consent to a medical treatment over a protégé only with the consent of guardianship authority; and the Health Care Act (Article 35) foresees the obligations of a health worker to inform a guardian authority if he/she considers that consent of a legal representative (both guardian and parents) to a medical measure is not in the best interest of the represented patient. Since medical experiments are not of the same relevance for the subject, as medical treatment for the purpose of curing, even more important would be to oblige the legally authorized representative to obtain consent of the guardianship authority before giving any further consent.

Hence, the fact is that neither international regulations nor the Medicines and Medical Devices Act. of Serbia which in details regulates clinical research, foresee this – we consider this an omission to be corrected. The literature contains the position by which request to engage guardianship authority needs to be rejected, since it can lead to prolongations of the research commence. Our opinion, however, is that if one subject decides of the submission of other subject to testing which are not medically necessary with certain risks against the subject (which always exist) – then the research commence has to wait and an opportunity has to be given to the guardianship authority to examine the whole situation. To the objection that a guardianship authority is medically incompetent and that ethical committees are sufficient, we have to respond that analogue to that legally authorized representatives are incompetent in this sense, too, as well as subjects, but again asked for their consent. Finally, ethical committees assess permissibility of the clinical research wider, from the aspect of numerous ethical and medical principles; therefore, those cannot sufficiently focus on issues if a legally authorized representative gives a consent justifiably or unjustifiably on behalf of the represented person. Their starting point is a consent as already given and they consider it in other context – was it given on the basis of correctly composed questionnaire, were the subject person and his representative sufficiently informed, etc. (Articles 64 and 73 of the Medicines and Medical Devices Act). On the other hand, guardianship authority has different assessment methods and criteria, other composition and experience in work, as well findings on the relation between the represented person and the representative; therefore, their previous assessment in this domain is considered important, besides the assessment done by ethical committees in a certain latter stage. Finally, if participation in researches can, by the opinion of experts, positively reflect upon the health of legally incompetent subject or it is in his/her interest for other reasons, it should not be suspected that position of his guardianship authority will be positive. The position of the guardianship authority will not be as such only if participation in researches is really problematic from the aspect of represented person and its representative for some reasons intends to give its consent, particularly when the represented person is opposing to that.

The following question imposes this: can a legally authorized representative give consent for participation of a represented person in a clinical research if such person is opposing to it, even after the assessment that it is in his interest? Reasons for this can be plain ones – ex. fear of a child from "people in white", etc. The Medicines and Medical Devices Act gives an answer to this question: consent is acceptable only if it is an expression of assumed will of legally incompetent persons (Article 64 and 66). Therefore, *argumentum a contrario*, their discontent cannot lead to duly valid consent of the legal representative. Regulations of certain states [23], as well some international regulations [24, 25], explicitly foresee that besides the consent of a legal representative, consent of a minor is also necessary; and that the rejection of participation in researches by such subject has to be respected. Exception is allowed if out of research no therapy exists for minor's illness, or minor's therapeutic benefit is in prospect. If elder children are opposing to research, the researcher needs to obtain a license for continuation of an experiment from scientific or ethical committees. Finally, by the Serbian Family Act (Article 62) and the Health Care Act (Article 35), a minor who turned 15 (and capable of reasoning) can individually give consent to a medical measure, and other legally incompetent persons should be involved in the process of decision making related to its undertaking – therefore, there is no reason not to take into consideration the opinion of those persons also in relation to participation in clinical researches.

Voluntary consent

Ban to subject someone to a clinical research or experiment without its free-will consent is foreseen by international [26–28], as well as national legal acts (commonly, by constitutions) and means respect of individual's autonomy [29] and right of every human being to self-determination [30]. The Constitution of Serbia [31] guarantees that "no one can be ….. subjected to medical or scientific experiments without his consent given by free will" (Article 25). This means that expression of will, representing the consent of the subject, must not have any shortcomings, i.e. there has to be harmony between internal and expressed will of the subject. Causes of the disharmony can be numerous.

1. Consent of the subject or his legal representative can be a consequence of fraud, threat or coercion by a researcher or a third person, and therefore it is neither free will nor valid. That originates both from the Guideline, forbidding coercion or other inappropriate impact on the subject (point 4.8.3.); also, from the analogue enforcement of the Serbian Obligations Act referring to expression of will in contracts (Ariticle 60–65, 112 and 117). Such expression of will can be made void, since it is not in harmony with the real expression of subject's will, while person obtaining consent in this way shall also be responsible for that. Hence, it is important to stress that this is right, but not also an obligation of the subject, and therefore its implementation is not obligatory (Article 112 of the Obligations Act).

2. Threat against the subject, however, may not always be an explicit one. It happens that some subjects who are in a dependent relationship with the researcher give their consent under the impact of fear from negative consequences of rejection – although not directly threatened by the researcher. Those, for example, can be medicine students or clinical staff to whom the researcher is a superior, as well as persons whose physician he/she is. In order to prevent this situation, it would be good to exclude the researcher from the process of all or at least such subjects' recruitment; and, this task should be given to an appropriately qualified individual independent on this relationship. Since this is not an easily feasible requirement in countries having low research resources, the other option is to eliminate the mentioned subjects from the list of possible subjects. The Serbian Medicines and Medical Devices Act (Article 63) selected the second option, foreseeing that persons whose free-will consent to participate in clinical research can be influenced by coercion or some other way of impact – cannot be participants of those. The Guideline (point 1.61.) classify this category of subjects as vulnerable subjects, i.e. those for who it is presumed that have diminished ability to protect one's interests manifested by a compromised capability to give voluntary consent to participation in an experiment [32]. Beside them, it is possible also that consent of other categories of vulnerable subjects is not essentially free will due to fear of negative consequences of rejection, and that should be taken care of [33].

3. The right to annul consent belongs also to the subject giving it in deception, where he got under no influence of others, personal or others guilt. Although convinced that he understood well all in relation to forthcoming research, it may happen that the subject got incorrect idea of the real situation and as such gave the consent which for this is not duly valid. This and the next quality of the consent are closely related, since one of the aims of subject's informing before the consent is to be given is exactly to remove any possible deceptions.

4. Finally, consent has to be given seriously, not in a joke, and this is guaranteed also by the requirement to have it formally, i.e. in written, signed and dated, i.e. given before a witness if the subject is not able to read (points 4.8.8. and 4.8.9. of the Guideline and Article 61 of the Medicines and Medical Devices Act).

Informing the subject before giving the consent

The next term of consent fulfillment validity which is required by all international and national regulations, is that a subject has to be informed about what he/she actually accepts prior to the clinical trial participation. This consent is in short named "informed consent". Some regulations, such are international conventions dealing with the problem of human rights, stay at the stage of proclamation – not entering into the details when it is actually considered that this term is fulfilled [Convention on Human Rights and Biomedicine (Article 16); Universal Declaration on Bioethics and Human Rights UNESCO (Article 6), etc.]. International and national regulations of clinical research involving human subjects,

however, elaborate this issue in details. On the basis of the analysis, we conclude that a subject can be considered informed if two conditions are cumulatively fulfilled: one of objective and the other one of subjective character. Objective condition is fulfilled if the subject is provided with all information necessary to overview the situation where he will get into and by this make a decision of consent. Subjective condition means that the obtained information is well-understood by the subject.

Objective condition

It is very obvious in international regulations related to clinical research involving human subjects that different manners that regulate what the subject has to be informed about and in what scope in order to consider his/her consent informed. Some of those determine the scope and the object of informing in an abstract manner, while others concretely list types of information the researcher has to present to the subject [34].

By the Nuremberg Code, the subject can give a consent which is considered informed if he/she sufficiently knows of "the nature, duration and purpose of the experiment, the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his/her health or person which may possibly come from his/her participation in the experiment" and if he/she understood provided information.

The Declaration of Helsinki stresses the need for subject's adequate informing, necessity of provided information understanding and provided full freedom when consent is being given (Article 24). The object of informing is set a bit wider in this Declaration than in the Nuremberg Code and can purport duty to inform the subject about: "aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study".

The Directive 20/2001 of the European Parliament and the Council from 2001 [35] underlines that the requirement for informed consent is fulfilled if the subject was duly informed on the "nature, significance, implications and risks of the study" [Article 2, par. 1, point (j)].

According to the International Ethical Guidelines for Biomedical Research Involving Human Subjects, informed consent exists if it was given by the competent subject who adequately understood necessary information which was provided (Guideline 4). This document differs from the previously mentioned because it in details regulates what is necessary information that a researcher has to present to a potential subject, giving list of 26 points.

The guidelines for Good Clinical Practice [36] do not define subject's informing as a short-term act, but as "a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate." As the previously mentioned document, the Guidelines also do not just abstractly determine the scope and the content of the right to be informed (point 4.8.10.). Those elaborate the subject of informing also through indication of a wide list of 20 information to be presented to the subject.

On the basis of the presented we could, above all, conclude that there is a disharmony in respect of terminology used in international regulations to determine scope and object of the obligation to inform the subject, as well as that quite a few regulations define this obligation more concretely. The obligation to inform is mostly defined abstractly and requires more precise definition; this is obviously left to a person obtaining the consent. At the end, this can lead to selective and by subjective criteria chosen scope and object of subject's informing. The space left for assessment in each individual case with how much information the level of "adequate", "necessary" or "sufficient" was reached can endanger reaching the quality for the informed one and by this duly valid subject's consent reflecting negatively in respect of his rights. On the other side, such regulations neither do sufficiently protect interest of researchers who can be treated as responsible for infringement of the obligation to inform the subject.

Under the Serbian law, the scope and object of subject's informing were determined within the Health Care Act – if it is about medical experiments (Article 38), and the Medicines and Medical Devices Act – if it is about clinical trials of medicines (Article 2). The first mentioned foresees that a patient over who a medical experiment is performed has to be "sufficiently informed about the sense, goal, procedures, expected results, possible risks, as well as inconvenient accompanying circumstances of the experiment"; the other mentioned defines informed consent as written statement of the subject "which is given voluntarily after duly informing on the nature, significance, consequences and risk to health". The Medicines and Medical Devices Act in its Article 59 refers also to implementation of already analyzed Guidelines. The mentioned indicates that the Health Care Act determines the scope of an obligation to inform the subject slightly narrower than the Medicines and Medical Devices Act (sufficiently informed is less than duly informed), while the scope of information which are object of informing are determined slightly wider.

Having in mind recognized differences, the question is raised: which legal text the researcher should follow performing the duty to inform the subject, as clinical trails are a certain form of medical experiments? Since in the area of clinical researches the Health Care Act has a character of general one (*lex generalis*), and the Medicines and Medical Devices Act of special one (*lex specialis*), the obligation of informing for the purpose of clinical research should be harmonized with the second mentioned which refers to implementation of the Guideline; therefore, a researcher in Serbia has the obligation of duly informing of the subject about all concrete information foreseen in the Guideline. In this way, respect of autonomy of potential participant in clinical research is fully ensured, as well as credibility of the researcher; therefore, we could conclude that the scope and object of the obligation to inform the subject is adequately and widely set in the Serbian law.

Subjective condition

Fulfillment of just analyzed, objective condition of the informed consent, i.e. providing necessary information to a subject – is not enough, if the subject did not understand it. Therefore, most of the referred regulations particularly underline the necessity to fulfill subjective condition, too. Some researches with this topic show, however, that in practice exactly fulfillment of this condition lacks [37–39], and providing consent to access the study is made equal to fulfillment of its objective, but the formal side of its validity – by communication of necessary information with signing of proper form. Obtaining essentially informed consent, however, has to have features of a process comprised of the procedure of information repetition, its additional clarification, responding to questions, etc. – all to the end of cognition that those are clear to the subject (point 4.8.7. of the Guideline). Important way to achieve this goal is to use words and expressions understandable both for the medically "illiterate" subject (point 4.8.6. of the Guideline). Some studies [40] showed that use of certain methods in order to improve understanding of provided information, like multimedia presentations or extension of the form intended to inform the subject, did not give the expected results. On the other hand, extended discussion on the relation researcher-subject proved as the most efficient way to improve understanding, as well as the use test method, i.e. asking for a feedback in order to check was the provided information understood well. Therefore, with the aim to reach legally and ethically acceptable and essentially duly valid consent to include people in clinical research, we suggest implementation of these methods in the procedure of potential subject selection in Serbia.

Responsibility for conducting clinical researches with invalid consent

If the researcher approaches clinical research with no consent of the subject or with his/her consent not fulfilling the mentioned conditions to be considered duly valid – the issue of researcher's responsibility will be raised, and it can be civil, criminal or both [41].

a) Civil responsibility means obligation of the researcher to compensate material and non-material damage suffered by the subject for being subjected to the clinical research without any or duly valid consent, and it is a fault of the researcher. It is an infringement of personality right. The researcher can't insure him(her)self against the responsibility for this kind of damage, for reasonable causes. Mandatory insurance of the subject refers to possible damages he/she could suffer as a consequence of participation in research performed by law (Article 72 of the Medicines and Medical Devices Act and Article 38 of the Health Care Act), but not from the damage suffered due to its involvement in the research with invalid consent.

b) The second form of researchers' responsibility in this situation is a criminal one, that will be raised if his/her action has features of a criminal act under the name "Illegal Conduct of Medical Experiments and Testing of Medicaments", foreseen in many countries by the Penal Code, as in Serbia (Article 252) [42], in the group of criminal offences against human health. A person shall be responsible for it, if: 1) against regulations performs medical and other similar experiment or clinical testing of drugs against people; and 2) clones people or performs experiments with that objective. While ban to cloning has an absolute character, medical and other similar research involving human subjects or clinical researches of drugs can be performed and responsibility of the researcher shall be raised only if done against regulations. The Guideline (point 4.1.3.) explicitly foresee that researcher has to know and respect regulations applicable in this field. Since the fundamental condition foreseen by Serbian and international regulations for medical experiments is the subject consent (which has to have all the features mentioned in this paper to be considered duly valid) – for this criminal offence shall be responsible the researcher who commits this intentionally without such consent. By the law, criminal offence is committed by the final performance of the described action (a research with no duly valid consent, in our case), and it is not necessary to establish did any other consequence appeared [43].

Beside the mentioned criminal offence, a person who provided the consent of a subject (or his legally authorized representative) to do something, not to do something or suffer in clinical research, by use of coercion, force or threat, shall also be responsible for the criminal offence of coercion (Article 135 of the Penal Code).

Conclusion

On the basis of everything presented in the paper we would like to make several conclusions.

Firstly, it is of tremendous importance for researchers to precisely know which terms have to be fulfilled in order to consider consent to clinical researches duly valid: both for possible serious consequences to the autonomy and subjectivity of the subject and its right to self-determination in regard to its body, as well as for prevention of personal responsibility, and, at the bottom line, for successful finalization of planned researches – without these there is no progress in medicine and no survival of the humankind.

Secondly, it is necessary to have clearly and completely defined terms within the national legislation in order to make researchers aware what are the conditions; those also have to be formulated in cooperation with experts from areas of medicine, ethics and law, taking into the account standards set in international regulations in this field.

Thirdly, researchers shall fulfil terms for getting valid consent in the easiest way if these terms are stipulated within one legal document.

Having all in mind, we could note that at least one of the indicated prerequisites was surely fulfilled in Serbia: obviously cooperation with physicians, ethicists and lawyers existed when terms for subject's valid consent were defined; requirements contained in international legal and ethic documents were also taken into account. This is proved by the fact that Serbian medical law today requires fulfilment of wide span of

terms for duly valid consent of the subject when participating clinical research, and content of some of those terms is well-defined both quantitatively and qualitatively (ex. number and sort of information with which subject in Serbia has to be informed). Serbian regulations, however, have two shortcomings, resulting primarily from the omission of lawyers.

First, some of the terms are not fully defined and some have no sufficiently precise definition – this is underlined by the paper and its authors gave also concrete suggestions to amend and make subject regulations more precise (ex. suggestions regarding relation of legal competency, legal age and subjects reasoning capability; regarding the need to get consent of guardianship authorities in certain situations; regarding actions of persons unable to give consent and having no legal representative, etc.).

The second weakness of Serbian regulations related to clinical researches stems from the first one: in order to remove its incompleteness and impreciseness, it is necessary to consult numerous legal texts – this exceeds capacities of any physician–researcher. Therefore, we consider important changes and amendments of the basic law in this field – the Medicines and Medical Devices Act in ways suggested in the paper, in order to gather all rules in Serbia regarding the provision of the subject's consent in one place and by this enable undisturbed performance of researchers.

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R E F E R E N C E S

1. *Shuster E.* Fifty years later: the significance of the Nuremberg Code. N Engl J Med 1997; 337(20): 1436−40.
2. *Živojinović D.* The historical development and international regulations of clinical research involving human subjects. In: *Mićović M* , editor. The collection of papers from the International scientists' gathering under the topic Law and Service; Kragujevac: Faculty of Law; 2012. p. 677−97.
3. *Radišić J.* Professional responsibility of medical staff. Belgrade: Institute for Social Sciences; 1986. (Serbian)
4. *Ivović N.* Saglasnost za eksperimentalne medicinske tretmane. Pravni život 2004; 53(9): 339−51. (Serbian)
5. *Živojinović D.* Requirements of ethical justification of clinical research. Novi Sad: Collection of papers of the Law Faculty; 2012; 46(1): 331−47. (Serbian)
6. Official Gazette of RS 107/05, 72/09, 88/10, 99/10, 57/11. (Serbian)
7. Official Gazette of RS 30/10, 107/2012. (Serbian)
8. Official Gazette of RS 18/05, 72/11. (Serbian)
9. „Official Gazette of SFRY" 29/78, 39/85, 45/89; „Official Gazette of SRY" 31/93; „Official Gazette of SM" 1/03. (Serbian)
10. Official Gazette of RS 2008 28/08. (Serbian)
11. The Nuremberg Code. Trials of War Criminals Before the Nuremberg Military Tribunals Under Control. Washington, DC: US Government Printing Office. 1949.
12. *Vodinelić V.* Civil law - Introduction to the civil law and its general part. Belgrade: Union University - Law School, Public Company Official Gazette; 2012. (Serbian)
13. *Stojanović D, Antić O.* Introduction to the Civil Law. Belgrade: Belgrade; Faculty of Law; 2004.
14. *Appelbaum PS, Grisso T.* Assessing patients' capacities to consent to treatment. N Engl J Med 1988; 319(25): 1635−8.
15. *Radišić J.* Medical Law. Belgrade: Nomos; 2004.
16. *Tatić-Klajn V.* Children as subjects of biomedical researches or experiments from the perspective of of medical, ethical and legal considerations. Pravni život 2009; 529(9): 837−54.
17. Official Gazette of RS 2009 72/09.
18. *Planojević N.* The property law in practice. Kragujevac: Faculty of Law, Institute for Legal and Social Sciences; 2012.
19. *Coots TJ, Shakur H.* Consent in emergency research: new regulations. Emerg Med J 2005; 22(10): 683−5.
20. *Simar R, Johnson VA.* Pediatric informed consent. Challenges for investigators. Appl Clin Trial 2002; 7: 3−10.
21. Wirgley A. Proxy consent: moral authority misconceived. J Med Ethics 2007;33: 527−31.
22. *Mason S, Barrow H, Phillips A, Eddison G, Nelson A, Cullum N*, et al. Brief report on the experience of using proxy consent for incapacitated adults. J Med Ethics 2006; 32:61−2.
23. A Guides of the British Medical Association (BMA). Online Application System. Available from: http://www.bma.org.uk/
24. *World Medical Association.* World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Postgrad Med 2002; 48(3): 206−8.
25. *Council for International Organizations of Medical Sciences.* International ethical guidelines for biomedical research involving human subjects. Geneva, Switzerland: World Health Organization; 2002.
26. UN General Assembly. International Covenant on Civil and Political Rights; 16 December 1966, United Nations, Treaty Series. Available from: http://www.unhcr.org/refworld/docid/3ae6b3aa0.html [accessed 20 February 2013].
27. Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on human rights and biomedicine. Oviedo: Council of Europe; 1997.
28. General Conference of United Nations Educational, Scientific and Cultural Organizations. Universal Declaration on Bioethics and Human Rights. Paris: UNESCO; 2005.
29. *Childress JF.* The Place of Autonomy in Bioethics. Hastings Center Report 1990; 20(1): 12−7.
30. *Živojinović D.* Consent on clinical research: notion and grounds for the consent, and content of subject intended information. Kragujevac: Faculty of Low; 2012. (Serbian)
31. Official Gazette of RS 2006 98/06.
32. *Grady C.* Vulnerability in Research: Individuals with Limited Financial and/or Social Resources. J Law Med Ethics 2009; 37(1): 19−27.
33. *Živojinović D.* Ethical dilemma of globalization of clinical research. Pravni život 2012; 555(9): 537−52. (Serbian)
34. *Del CMG.* Informed Consent for Medical Treatment and Research: A Review. Oncologist 2005; 10(8): 636−41.
35. Directive 2001/20/EC of the European Parliament and of the Council. Luxembourg: Official Jurnal of the European Communities; 1.5.2001; 1996.
36. European Medicines Agency. ICH Topic E 6 (R1). Guidelines for Good Clinical Practice, CPMP/ICH/135/95. London: European Medicines Agency; 2002.
37. *Joffe S, Cook E, Cleary PD, Clark JW, Weeks JC.* Quality of informed consent in cancer clinical trials: a cross-sectional survey. Lancet 2001; 358(9295): 1772−7.

38. *Lynöe N, Sandlund M, Dahlqvist G, Jacobsson L.* Informed consent: study of quality of information given to participants in a clinical trial. BMJ 1991; 303(6803): 610−3.
39. *Zhang D, Yin P, Freemantle N, Jordan R, Zhong N, Cheng KK.* An assessment of the quality of randomised controlled trials conducted in China. Trials 2008; 9: 22.
40. *Flory J.* Interventions to Improve Research Participants' Understanding in Informed Consent for Research. J Am Med Assoc 2004; 292(13): 1593−1601.
41. *Mujović-Zornić H, Petrović Z.* Responsibility of Health Institutions for Harms as Consequences of Treatment. Vojnosanit Pregl 2012; 69(8): 692−9. (Serbian)
42. Official Gazette of RS 85/05, 88/05, 107/05, 72/09, 111/09.
43. *Stojanović Z.* Comment of the Penal Code. Belgrade: Savremena administracija; 2009. (Serbian)

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