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Informed Consent – as a Protective Tool of the Right to Autonomy and Dignity of Human Subjects Participating in Biomedical Research, in the Context of the International Law of Human Rights

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Abstract: *Informed consent is an instrument aimed at protecting the right to autonomy and dignity of human subjects participating in biomedical research. In this article, a series of forms of consent are presented, which together with informed consent, ensure the observance of these rights in accordance with the international law of human rights: delegated consent, broad consent and consent assent (in the case of minors). A series of normative acts issued by the United Nations, aplicable at a global level, or as part of the normative system of the Council of Europe and of the European Union, aplicable at an European level, are analyzed, as well as their reflection in the normative acts enforced, at a national level, in Romania.*

Keywords: *informed consent; research on human subjects; dignity; autonomy.*

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Introduction

The respect for autonomy is a fundamental ethical principle in both biomedical research and therapeutic practice. A valid consent is given by a person who is capable of decision-making and is fully informed regarding the purpose and the objectives of the research, the risks to which it is subject and the potential benefits, both to themselves and to others, including all of humanity, and who voluntarily decides to participate in that research (Ciucă, 2009). The purpose of obtaining the informed consent (IC) is to ensure that the subject's participation is voluntary, generally altruistic, that the decision belonged entirely to the subject and was taken in full knowledge of the facts. Obtaining informed consent ensures the integrity of the research within the researcher-subject relationship and provides legal protection to the researcher and the research team against the risks on which the subject has been informed that may intervene and upon which they have agreed to (or maintained their agreement) în order to participate in the research.

IC is a necessary requirement for the conduct of any research that includes human subjects in an ethical manner (Alexa-Stratulat et al., 2018). In practice, obtaining informed consent aims to inform subjects about the research, including the purpose, objectives, methods and procedures used, the scientific importance and practical usefulness of the results, the risks and benefits that the subject can expect, the fact that the decision is and must be voluntary and that they may withdraw from the research at any time, without in any way affecting their relations with the research team, the institution that is implementing the research project or is providing the funds for the research, and - in biomedical research – losing their right to treatment, which will be further granted in accordance with the available and non-experimental standards of the implementing institution (Shahnazarian et al., 2017). The subject shall be informed of their rights and duties, including those relating to maintaining the confidentiality of their participation in the research, even when the information may reveal malfunctions, unless the criminal investigation bodies request access to the information. The purpose of obtaining informed consent is to ensure that the rights of the participants are respected, even when they involve risks, that sufficient information has been provided in clear and appropriate language to enable the subject to assess their understanding, what their situation will be during and after the participation in the research and to express their agreement in full knowledge, as far as their level of understanding allows. Regarding informed consent, which is a process rather than a procedure, researchers have a duty to ensure, throughout the research, that the participation of the subjects is

still voluntary and that the subjects are fully aware of what is happening to them or could happen to them in the next stages of the research.

Terminological specifications in the field of "informed consent"

From an administrative-technical point of view, informed consent in clinical research „is the written decision, signed and dated, of a person capable of giving their consent or, in the case of a person who is unable to do so, of their legal representative, to participate in a clinical study, taken voluntarily and knowingly, after receiving all the necessary information about the nature, significance, consequences and possible risks, as well as the necessary documentation" (Purcaru et al., 2012).

IC în research is the process by which the research participant agrees to participate in the research after being informed of the procedures, risks, and benefits (Bulger, 2002).

At the same time, the concept of informed consent defines the process of obtaining the subject's agreement regarding their participation, fully voluntary and based on their own decision, taken in an informed manner, in research - or in a therapeutic act. It is, at the same time, a process, as well as a legal document signed by the consenting person or their legal representative, in case they are prevented from consenting (Purcaru et al., 2012).

Faden and Beauchamp (1986) define the process of obtaining informed consent as an expression of concern for protecting and facilitating the autonomous or self-determined choices of patients and subjects (în the research – a.n).

IC can be transformed into an instrument of normative compliance with regard to human rights, when the practice of obtaining IC is interpreted in a formalistic way, by referring to strict rules for obtaining IC and their formalization (Maclean, 2009). Consent has the role of creating a legal barrier to control the process of providing permission (Larry, 1996).

The Nuremberg Code defines the process of obtaining informed consent as being one and the same with enforcing the respect for individual autonomy by researchers.

Normative acts that regulate the use of informed consent in research

a. Relevant normative acts at global level

The World Medical Association Declaration on Ethical Principles for Medical Research Involving Human Subjects, Helsinki, June 1964

In research involving human subjects capable of providing IC, each of them must be adequately informed about the purpose, methods and data sources of the research, possible conflicts of interest, the institutional affiliation of the researchers and the sources of research funding, the effects, the benefits and anticipated results of the research, the potential risks of the study, including any discomfort that may occur during or after the study, as well as any other relevant aspects of the research that the investigator considers important for the participant to know. According to the same Helsinki Declaration, but also to the relevant European Commission Directives (Directive 2001/20 / EC and Directive 2005/28 / EC), that have been issued aș an effect of this declaration, the investigator is obliged to inform the participant of their right to refuse to participate în the research or to withdraw from the research at any time, without any negative consequences (Kim & Miller, 2014) for the subject.

The Convention on Biological Diversity (1992)

The Convention on Biological Diversity (1992), in Article 8 (j), states that "access to the traditional knowledge, innovations and practices of indigenous peoples and local communities should be subject to prior informed consent or prior acceptance by the holders of such knowledge, innovations and practices mentioned above ".

The parties to the Convention considered it necessary to introduce informed consent in the above-mentioned article, given the unique value attributed to traditional knowledge on biodiversity, as well as existing practices in local communities. Basically, the convention requires that the use of traditional knowledge related to the environment, but also to the health of the population, be treated in a manner similar to how access to scientific knowledge is made, when this is possible, and especially when this knowledge is an element of immaterial heritage specific to local communities.

When traditional knowledge belonging to local communities is used and especially when the use of this knowledge is made for the purpose of preserving and protecting the biodiversity of affected sites, considered sacred by that population - whether we are talking about archaeological sites,

monuments of any kind or surfaces of land, localities and other geographical elements, landforms waters etc. -, the informed consent of the interested community must be obtained to such an extent that there is no doubt that the members and, in particular, the representatives of that community have understood the exact nature, effects and dimensions of the use of that knowledge, innovation and practice.

In the use of traditional knowledge, innovation and good faith practices, the principle of subsidiarity should be applied - in other words, negotiations between the implementer and local communities should be conducted in such a way that the decision obtained is representative at the lowest possible level, i.e. with the widest and most informed participation of the members of the interested community. In this situation, the decision-making process will seek to empower the community - both its representatives and its members in general - to make decisions about what concerns them directly.

Measures such as the relocation of the population or the removal of the members of a community from their traditional locations should not be enforced but, on the contrary, taking any such measures should be based on an informed consent obtained directly from the persons affected by the measure, except, of course, în case of situations of force majeure.

International Covenant on Civil and Political Rights and International Covenant on Economic, Social and Cultural Rights (both adopted in 1966)

The International Covenant on Civil and Political Rights (ICCPR), together with the International Covenant on Economic, Social and Cultural Rights (ICESCR) and the Universal Declaration of Human Rights (UDHR), is part of the International Charter of Human Rights. The International Covenant on Civil and Political Rights (ICCPR) is a multilateral treaty adopted in 1996 by the United Nations General Assembly - Resolution 2200A (XXI). Through this pact, the signatory parties undertake to respect and defend the civil and political rights of individuals, the most important of which are "the right to life, freedom of religion, freedom of expression, freedom of assembly, electoral rights and the right to an appropriate procedure and a fair trial".

The two conventions we discuss in this section (The International Covenant on Civil and Political Rights and The International Covenant on Economic, Social and Cultural Rights) do not use the notion of informed consent but only that of consent - but later, in the activity of the Committees set up to implement their provisions, the idea of informed

consent has been constantly referred to, which, in our view, is an evolution of both the doctrine and the practice of obtaining consent. More specifically, the members of the above-mentioned committees felt the need to clarify the type of consent - namely the informed consent, in order to differentiate it from the delegated or the presumed consent, which may appear in certain situations and which we will discuss later in the context of this paper.

In the content of the International Covenant on Civil and Political Rights appears the concept of consent with reference to marriage (art. 23 para. 3) and, respectively, with reference to participation in various research projects - including biomedical ones - or the situation when a person becomes the subject of medical treatment (art. 7). We are talking about the status of a subjective right to decide about one's own life, both in terms of one's civil expression - as in the case of marriage - and one's own health condition - as in the case of treatment or research.

The United Nations Human Rights Committee has been set up to monitor the implementation of the International Covenant on Civil and Political Rights by State Parties. It functions as a separate body of the United Nations Human Rights Council and is an independent body of experts (UN, n.d.). The Committee shall examine the reports of State Parties regarding how the provisions of the ICCPR are being implemented and the manner in which human rights are effectively protected in the countries that are a parties to the Convention.

In the context of presenting the two conventions and, in general, the acts issued within the United Nations system and aimed at the protection of human rights, we refer to the General Commentary of the Human Rights Committee (1994). The Committee points out that, although art. 7 of the International Covenant on Civil and Political Rights expressly prohibits the conduct of medical or scientific experiments without the free consent of the subject, greater attention is needed from states for the compliance with this provision. The Committee's observation was made in 1992 and published in 1994, in a collection of General Comments and Recommendations adopted by the oversight bodies for the implementation of the International Charter of Human Rights.

In art. 4 of the International Covenant on Civil and Political Rights (ICCPR) there is a list of rights and freedoms from which states cannot derogate (ICCPR, n.d.). The rights provided for in the Convention, as stipulated in the cited article, may be limited only under special conditions, defined as states of public emergency which constitute direct threats to the situation of a country or a nation. Even in emergencies, derogations from the right to life, the prohibition of torture or slavery, the right of the

individual to citizenship, freedom of thought, conscience and religion, and the right not to participate in scientific experiments are not permitted without express consent.

In the near future, we consider it necessary to have a wide-ranging discussion worldwide - both in the bioethical and in the legal community - on the compatibility of measures such as compulsory vaccination in special situations, such as the COVID-19 crisis, with the provisions of the treaties. Even though the European Court of Human Rights has ruled in favor of states regarding the compulsory vaccination of certain categories of professionals directly involved în public health emergency decisions, the generalization of such a measure to the whole population, as in the case of Austria, can be interpreted (Ignatescu, 2017) as a derogation from the Convention, as long as there may be cases of persons who are not în a situation where public interest can be invoked, being - for example - inhabitants of isolated communities, who have little or no interaction at all with the general public.

Of course, the experience of the current pandemic will be a starting point for such debates and, we believe, will eventually lead to the emergence of normative acts regulating the limit of public interference in private life, justified by the interest in public health.

The second pact brought into question, the International Covenant on Economic, Social and Cultural Rights, uses the notion of consent - without making direct reference to that of informed consent - in the context of art. 10 para. 1. This paragraph emphasizes the need for free consent to marriage in the general context of the protection of the right to family life - the family being considered a fundamental structure of society, with responsibilities for the care and education of their minor children or of those who are dependent on the care offered by the spouses.

In the context of art. 11 para. 1, by which the signatory states undertake the obligation to recognize and defend the right of every person to a number of adequate standards of living for themselves and their family, free consent is considered important - ensuring the right to consent may be the subject of international cooperation in defense to the continuous improvement of living conditions.

States undertake a positive obligation to ensure that the right to consent is not violated, either directly or indirectly, through the economic or social conditions specific to a each country (United Nations General Assembly, International Covenant on Economic, Social and Cultural Rights, Chapter IV - Human rights).

International Ethical Guidelines for Biomedical Research Involving Human Subjects - adopted by the Council for International Organizations of Medical Sciences (CIOMS), November 2002

Another relevant document regarding the ethical rules regarding research on human subjects is the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) in 2002.

Even if the document does not have the value of an international treaty (Florea, 2017), but only of a guide of ethical practices (recommendations) in biomedical research, we refer to this document due to its value as a practical tool in implementing international acts regarding the respect for human rights in biomedical research and for the possibilities it provides for building ethical policies in the field of research on human subjects - both nationally and internationally.

The document states that all research involving human participants must be carried out in a manner that ensures respect and consideration for the rights and well-being of research participants and the communities in which the research takes place. Respect for the rights to well-being, dignity and self-determination requires the informed consent of all participants and the minimization of the risks they are exposed to, as well as the reasonableness of the risks assumed by the participants, in accordance with the importance of the research. However, the document tells us, there may be situations when, despite the social and scientific value of the research and even în the presence of an informed and voluntary consent, the risks are so great that they are not justified. This is the case, for example, with studies involving the voluntary infection of participants with the pathogens of Anthrax or Ebola.

Informed consent must be obtained through a process that ensures the full information and acceptance of participants, both at the time of enrollment and throughout the research, including after its completion. We emphasize that, according to this guide, informed consent does not only mean a document signed by the participant - which, although necessary, is only part of the process of obtaining informed consent.

The researcher must ensure that the participant has freely consented, after understanding - within the limits of their cognitive abilities - the meaning and implications of the medical research act to which they are subjected and that the voluntary nature of the subject's participation in the research is obvious, with no other factors than the subject's own will having determined their participation.

According to this ethical guide, the obligation to observe informed consent rests with researchers who carry out certain research, as well as with health authorities, sponsors, or any other institution significantly involved in the conduct of research. Research subjects - both at the individual and community level - should be involved in a meaningful participatory process at all stages of the research, both in its design - in the design of the informed consent process - and in the monitoring of the research implementation and of the risks to which the participants are subjected - therefore also in the process of disseminating the results. Informed consent, obtained individually from each participant, is necessary în order to eliminate any pressure or influence that the subject may be subjected to by other individuals or the community, regardless of the perceived and estimated value of the results for the well-being of the individuals themselves, of other persons or of the community to which the subject belongs.

Members of the community to which the subjects belong should be invited to participate in the process of obtaining informed consent and to ensure that the documents that will be made available to the subject and that represent the written expression of informed consent are written in a language accessible to the subject, and that the meaning of the terms used is the same as the meaning of those terms in the subject's reference community. Guideline 9, which refers to individuals who are able to consent, stipulates the obligation of researchers to make available to the potential participants, even before their admission în the research, all relevant information on the research and especially the risks of which researchers are aware. Researchers are also required to provide subjects with the opportunity to consent or refuse to participate in the research and, in addition, to ensure that their consent is informed and that their participation is free and voluntary.

An exception to this obligation may arise when the design of the research is approved by a research ethics committee (RECS), which states that obtaining informed consent is impossible due to certain particular situations in which the subjects find themselves - people with limited understanding etc. -, that there is a limited degree of risk to which they are subjected and that it is not possible to select participants with full consent. Such a situation may be the testing of active substances, intended to treat or improve the quality of life (Sandu & Damian, 2018) of people suffering and whose suffering per se limits their ability to consent (Alzheimer's, dementia, various other mental disorders).

In practice, the recommendations in these situations are primarily to avoid, as far as possible, including persons belonging to vulnerable

categories among the participants în the research - especially those who do not have the capacity to consent or whose vulnerability may affect their decision. For the latter case, we mention, as an example, the prohibition of participatind in research, albeit on a voluntary basis, for persons incarcerated in prisons, because their decision to participate in the research may be influenced by those correctly or falsely perceived as having or being able to exercise discretionary power over them or, on the contrary, they feel it is compulsory to take risks, which they would not assume in a state of freedom, because of their own health condition, motivated by the hope - suggested or not by the researchers' representatives - of an early release from prison.

Even in the case of prior approval by an ethics committee, a process of obtaining informed consent or a new ethical evaluation is required in case of a change in any key elements of the research framework. If the participant, although able to express their consent, is unable to consent in writing due to illiteracy or locomotor or sensory disabilities, the consent is validly obtained by any means that can prove the reality and effectiveness of the obtained consent.

Guideline 10 refers to the way în which the modification or cancellation of informed consent can be provided. This recommendation reiterates the obligation for researchers to refrain from engaging in the implementation of any research on human subjects before obtaining the valid informed consent from each participant or their legal representative, or obtaining the express opinion of a research ethics committee thjat such a consent is not necessary. Informed consent may be revoked or amended at the request of the participant or on the initiative of the researchers, only after the latter has ascertained that there are no other means of protecting the subject, which would allow further research.

If it is necessary to change the informed consent, the process of obtaining it must be resumed in ways that ensure that the research subject has fully understood the changes to the situation to which they initially consented. When it is necessary to remove data or information from the consent process, a step necessary în the research process - for example, whether the subject will be included in the experimental group or in the control group, or if the context of the research is vaguely or slightly distorted in the case of research in the field of psychology -, these changes cannot be made without the approval of an ethics committee, obtained each time the experimental conditions change.

Even if research results are to be stored separately from informed consent, an external evaluator - including a member of the ethics committee

- must be able to identify informed consent documents without being able to access the subject's biological and biomedical data. According to Guideline 11 on broad consent to the storage of biological data, samples and tissue specimens for future research, the subject must be informed that the biological data or samples will be stored and could be used in future unspecified or as-yet-unforeseen research, and that the subject has the right not to accept their storage or future use, or that at a later date they have the right to request the destruction of the biological matrial or the deletion of data regarding their health condition.

Information on biological samples - especially human genetic material - is a sensitive topic, precisely because of the risk of its unethical use in genetic research, because the subject might disagree with the conduct or objectives of such a research. We mention the case of Henrietta Lacks, whose biological material was used in cancer research long after her death, without ever having been informed of thisl or asking for her consent (Beskow, 2016). Research using such biological materials, collected on the basis of broad consent and stored in cell and tissue banks, must be approved by an ethics committee.

If the purpose of the use of the left-over biological material, taken at the stage of making a diagnostic, is known at the time of sampling, informed consent becomes mandatory and cannot be replaced by broad consent. If material compensation is offered to the participants in the research, it must not exceed the expenses incurred by the subject for participating in the research and, in any case, must not be of such a value as to induce the wish to participate in the research for onerous reasons. This is especially true if the subjects come from vulnerable, low-income groups.

Guideline 15 clarifies the situation of minors who participate in a research, who, although do not have the legal capacity to consent - more precisely, their consent cannot be considered legally valid -, are required to state their agreement or disagreement regarding their own participation in the research, and the researchers are obliged to respect the possible disagreement of the minors, even if a valid delegated consent was expressed by the parents or legal guardians. The text distinguishes between consent and assent (provided by minors).

In the case of randomized clinical trials, subjects cannot be informed of their inclusion in the control or experimental group, and therefore the opinion of an ethics committee is absolutely necessary. The ban on leaving the patient untreated should also be taken into account and therefore placebo can only be applied to the control group unless there is no confirmed treatment for the disease in question. Otherwise, any innovative

treatment should be at least comparable with the usual treatment for the disease in question.

b. Relevant regulations at regional (European) level

Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, Oviedo, April 4th 1997

The Oviedo Convention provides for the obligation to obtain the informed consent of the participants in any type of research involving human subjects.

In Chapter II, art. 5, para. 1, 2 and 3, the Oviedo Convention expressly provides: an intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time.

The Convention stipulates the obligation of obtaining informed consent - usually expressed in a form that includes the written expression of consent - after informing the participant in advance about the purpose and objectives of the research, the potential benefits and risks, and the participant's right to withdraw from the research at any time. Informed consent must, in accordance with the Oviedo Convention, be based on voluntariness. In the case of persons who cannot personally consent, their participation in the research is conditioned by the existence of a direct benefit for the person or for the category of vulnerable persons to which they belong, as well as the non-existence of another way to obtain the necessary information for the research.

The Oviedo Convention is considered to be the first international act to protect human dignity, human rights and freedoms from the misuse of research in biology and medicine. The premise of the Convention is that the interests of the human being prevail over those of any other nature - including scientific ones - and therefore the development of science and technology must be possible only in ways that do not infringe on dignity and the interests of the human being, in particular those who participate directly in the research, but also those who will later benefit from the research results.

The convention stipulates a series of principles of good-practice, as well as a series of prohibitions governing the research activity in the field of medicine, so as not to infringe on the freedom and dignity of the human

being. These rules and prohibitions primarily concern the modalities and limits of participation în the research for subjects who cannot directly consent for various reasons, such as age, health condition, level of intelligence, information or culture etc.

As a general rule, the Convention stipulates the need for informed consent for the participation in research of any person who may consent. The rules established by the Convention concern, in particular, derogations from the principle of informed consent, and the contexts and measures to be taken when such a derogation is necessary. An important principle of the Convention is the prohibition of creating human embryos for the sole purpose of conducting experiments on them or taking fetal material for the purpose of conducting biomedical experiments, which would harm the dignity of the human being, but also of the human species (Zenelaj, 2018).

With regard to the idea of consent, its characteristics are similar to those of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) in 2002. These characteristics are: the absolute voluntary nature of participation in research, the informed nature of consent - whenever possible - or the observance of measures to ensure the protection of persons who cannot consent, the approval of the ethics committees, the possibility for the subject to withdraw from the research or to refuse a treatment whenever they want, even if they agreed in advance, regardless of the costs that this withdrawal may involve for themselves or others etc. The only exceptions to this rule are those of public order, when, for example, involuntary hospitalization is necessary in order to protect oneself or others (Andorno, 2005).

Consent for treatment must be express, it must be particulary adressed for participation in biomedical research, and the subject must be able to distinguish between participation in research and treatment. The participation of minors or persons belonging to vulnerable population groups in biomedical research may be permitted only when there is a real benefit to such persons. Adults who can consent must participate voluntarily, but the motivation for participation may be, within certain limits, the general progress of science, sometimes excluding personal benefits, even if the research is developed in the field of improving health.

Emergency medical interventions aimed at saving lives or preserving health are exempt from the obligation to obtain consent of any kind - informed or delegated - when the subject is unable to consent and there are no ways to contact their relatives. In this situation, we are talking about the idea of presumed consent, the desire of the subject to protect their life and

health being presumed only when it cannot be directly expressed. However, when the subject can express their will, they have the right to refuse treatment, even if the respective therapeutic intervention is considered by experts to be absolutely necessary to save their life or to maintain / improve their quality of life.

The Convention also expressly recognizes the person's right not to know, but the person's wish not to be informed must be expressly stated and cannot be presumed, even if certain elements of the patient's health condition have a high degree of scientificity, which would prevent a good understanding of one's own health condition.

The Convention prohibits the taking of organs or tissues that cannot be recovered from persons who cannot consent. A particular situation is that of minors, who can be presumed organ donors for close people with whom they have maximum compatibility and who can help save the lives of those concerned. However, the Convention limits this practice to the protection of minors who are unable to consent - especially when the child is unable to fully understand the consequences of donating tissues or organs, except for tissues that recover over time, such as in the case of bone marrow or bone tissue.

Post-mortem organ donation is also limited, with some countries requiring only family consent for organ harvesting from brain-dead people, while other countries - signatories to the Oviedo Convention - require that such a directive be given in advance by the person în question, as this is a form of expression of the person's will through legal acts regarding the permission to harvest their own organs for the purpose of transplantation in case of accidents leading to brain death (De Angelis, 2017).

Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings – adopted by the Council of Europe - ETS no. 195, Paris, 12.01.1998

The document seeks to ban human cloning, as well as other practices of a medical or biomedical nature aimed at infringing on the dignity of the human being or the diginity of the human species, as a result of technologies that have an impact on the specifics of human nature or condition.

Ad Hoc Group for the Development of Implementing Guidelines for Directive 2001/20/EC Relating to Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. 2008. Ethical Considerations for Clinical Trials on Medical Products Conducted with the Paediatric Population

This normative act clarifies the conditions în which minors can participate in clinical trials. The main provisions contained in the document regard the assent that the minor who cannot consent offers, in the context of a voluntary participation in clinical trials, in accordance with art. 29 (8) of the Clinical Trials Regulations. In a manner similar to the regulations set out in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Ad-hoc Group's Recommendations provide that the assent of the minor regarding their participation in clinical research is required. In the context of this document, the term assent should be understood as an expression of the will of the minor, which should have legal value, of course in accordance with consent expressed by their legal representatives.

The same normative act defines the term agreement - acceptance - which is not an expression of a legal requirement, although researchers are recommended to obtain the consent of minors at each stage of the research in which they participate. The application of the instrument called assent and the requirement of acceptance by the minor differs depending on the age and ability of the minor to understand the situation they are in, as well as the implications of the decisions they make for their own health condition. In addition to the expression of the agreement of will on the part of the minor, their participation in any clinical research is conditioned by the informed consent provided by their legal representatives. In parallel with the assent of the minor, their refusal to participate in the research is defined and called dissent - according to art. 32 (1.c) of the Clinical Research Regulations. The refusal to participate of the minor who is not fully able to understand the situation and the implications of their decision is not necessarily considered an expression of their opposition - dissent - to participation in the research. The refusal to participate - dissent - must be respected in accordance with Article 32 (1.c), as an equivalent to the lack of informed consent or informed refusal to participate in the research, as defined in art. 2 (2.21) of the Regulation. The refusal to participate in the research should be considered as such, even if it contradicts any consent from the legal representatives, due to the express requirement that the participation of the subjects in the research be of a voluntary nature.

As already presented, the two documents - the International Guide to Ethics for Biomedical Research Involving Human Subjects and the Rules of Good Clinical Practice -, are documents that establish the rules for conducting research on human subjects, the first targeting human subjects in general, and the second focusing in particular on the situation of minor subjects.

The analysis of the two documents can help us understand the evolution of the concept of informed consent and its applicability, from a general instrument for the protection of rights such as life and dignity, to a specific instrument for the implementation of clinical ethics, which should be in accordance with the values defended by the various human rights protection systems.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. JO L 121, 1.5.2001

The Directive of the European Parliament, in paragraph 3 of the explanatory memorandum, refers to the obligation of Member States to ensure special protection for persons who are unable to express legal consent to their participation in clinical trials. The involvement of these categories of people in clinical trials should be avoided whenever research can be carried out exclusively with the participation of those who can consent. The involvement of persons incapable of consent in any research - clinical or biomedical, in general - should be limited to those researches that can bring immediate benefits, in the sense of improving the health and quality of life of the subjects. The criteria to be considered are the relationship between the risks and the benefits of participating in research for all subjects, especially those who are unable to consent. This is justified by the fact that the participation of such a person in the research, although it can be considered voluntary, is outside their capacity to assess the risks and benefits - and therefore outside their expressive autonomy. Particular emphasis is placed on the participation of minors, children and adolescents in such a research, which cannot be done otherwise precisely because of the fact that therapies for these categories of people are being investigated, which show age-specific physiological features.

In the content of the normative act, more precisely in art. 2, emphasys is placed on the specifics of informed consent for participation in research, which must be in writing, dated and signed and be a direct

consequence of the nature, significance, consequences and risks of the individual participation in the research. If the person cannot consent, the written consent must come from their legal representatives, and if they cannot sign, but can consent, the verbal consent is sufficient. We note the similarity between these European regulations and those existing at an international level - with the specification that, in our opinion, the existing regulations at the European level bring clarifications to those aplicable at an international level in terms of their effective and efficient implementation.

The normative act in question also refers, in art. 2 para. k, to ethics committees - defined as independent bodies made up of medical and non-medical staff - whose responsibility is to protect the rights, safety and well-being of research participants, as well as to provide assurance to the general public, including by providing opinions on the research protocols, but also on the adequacy of the researcher's competence and skills regarding the specifics of the research.

Ethical aspects of clinical research in developing countries. Opinion of the European Group on Ethics in Science and New Technologies to the European Commission, 2003

Even if the document does not have a normative value in itself, we will refer to the opinion expressed by the European Group on Ethics in Science and New Technologies and addressed to the European Commission in 2003, precisely to make the link between the legal and the (bio)ethical component of our research, in an attempt to highlight a continuity between the two components.

Protection through legal instruments is, in fact, a set of values that have an intrinsic ethical nature. At the same time, ethical standards derive from the legal norm that distinguishes them for various social contexts. The opinion expressed in the analyzed document refers to human dignity and its social expression, through the principle of informed and free consent and respect for the right to integrity of the person.

Informed consent is a form of the expressive autonomy of the individual and not only of the deliberative one and, as such, its manifestation represents an inalienable component of the person's integrity, seen as coherent with themselves. Even if a person's decision can be considered illogical or in violation of principles such as sufficient reason, the expression of will remains a self-expression of the person and, as such, ensures their coherence with themselves, an is, in fact, a guarantee of the person's dignity.

The document we are analyzing at this point in our paper discusses the expression of informed consent in the context of respect for diversity

and the sensitivity that researchers must show towards the cultural specificity of the environment from which the research subjects come and which imprints the particularities of expressive autonomy on them. Cultural sensitivities can influence not only the acceptance or refusal of participation in the research, but even the acceptance or refusal of the therapeutic act itself. Patients from socio-cultural backgrounds who focus on pain resistance may be reluctant to take the therapeutic action, believing that coping with suffering and illness is a sign of their maturity or even superiority over those who easily resort to treatments or various other health care practices. The importance of education in general and health education in particular, the level of understanding of scientific information, but also the social environment in which the subject lives is also emphasized.

c. Relevant normative acts at a national level

The transposition into the Romanian legislation of the directives of the European Parliament and of the European Commission on the compatibility of the laws and administrative acts of the Member States on the application of good clinical practice in conducting clinical trials on human subjects was made by orders of the Ministry of Public Health no. 903/2006 and 904/2006.

The main normative acts in the Romanian legislation that regulate the obligation of the informed consent of the patient are represented by: Law no. 95/2006 on the reform in the fields of health and justice and Law no. 46/2003 on patient rights.

Order of the Ministry of Public Health no. 903/2006, for the approval of the principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, Published in the Official Gazette of Romania, no. 671 of August 4th, 2006

The Ministerial Order includes, in the Annex, the text of Commission Directive 2005/28 / EC of April 8th, 2005 on detailed principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, published in the Official Journal of the European Communities, no. L 91 of April 9th, 2005.

References to the informed consent in this normative act are correlated with the citations for excluding some participants from the

research for the lack of or validly expressed informed consent, as well as for the lack of the voluntary nature of participation în the research. Also, the content of the Ministerial Order refers to the obligation of researchers to respect the confidentiality of data on research participants.

Law no. 95/2006 on the reform in the fields of health and justice

In the content of Law no. 95/2006 regarding the reform in the fields of health and justice, the references to the informed consent are made in art. 101 (1): "Private emergency medical care in the pre-hospital phase is provided by private ambulance services, based on a direct contract with the beneficiary, with their private insurer or at the direct request of the beneficiary or any other person, with their consent" and, respectively, in art. 144 (1): "The collection of organs, tissues and cells of human origin from the living donor is done under the following conditions: a) the collection of organs, tissues and cells of human origin, for therapeutic purposes, can be performed from living adults who have a full capacity to exercise their will, after obtaining their informed, written, free, prior and express consent, according to the model form approved by order of the Minister of Health. It is forbidden to take organs, tissues and cells from persons who do not possess discernment; b) the consent is signed only after the donor has been informed by the doctor, the social worker or other persons with specialized training on the possible risks and consequences on a physical, mental, family, professional and social level, resulting from the act of collecting the sample; c) the donor may revoke their prior consent, until the moment of collection of the sample; d) the taking and transplantation of organs, tissues and cells of human origin as a result of the exercise of a physical or moral constraint on a person are prohibited; e) the donation and transplantation of organs, tissues and cells of human origin may not be the subject of legal acts and deeds in order to obtain a material or other type of benefit; f) the donor and the recipient will sign an authentic document stating that the donation is made for humanitarian purposes, is altruistic and does not constitute the object of legal acts and deeds in order to obtain a material or other benefit, according to the model form approved by order of the Minister of Health; g) the donor will be exempted from the payment of the hospitalization / hospitalizations related to the donation, as well as from the costs related to the regular post-donation medical examinations".

The above-mentioned articles are in accordance with the international regulations that we have discussed in the previous paragraphs, as such we will not insist on their content, doing only our duty to mention them.

An important direction for understanding the particularities of the process of obtaining consent in the case of minors is represented by art. 145 (1), which takes from the European regulation the prohibition of sampling "organs, tissues and cells from potential minor donors, except in the cases provided for in this law". This law clarifies, in para. 2 of the same article, that, with the exception of the provisions of the previous paragraph, the collection of medullary or peripheral hematopoietic stem cells from minors can only be done with the consent of the minor, if they have reached the age of 10, and with the written consent of the legal representative, respectively of the parents, guardian or curator, according to the form approved by order of the Minister of Health".

Article 150 of the same law establishes the obligation of obtaining informed consent from the recipient of the organ transplant as well, unless he is unable to consent. We are once again in the de facto situation of presumed consent, when it comes to an emergency intervention, which can save the patient's life. We mention that in art. 150, reference is made to the obligation to use the form of informed consent approved by ministerial order, which may be a predisposition to formalize informed consent and transform it from a deliberative process into a purely administrative one.

Law no. 46/2003 on patient rights

In the content of Law no. 46/2003 on patient rights, the relevant legal texts on informed consent are contained in art. 4, 5 and 6 of Chapter II, entitled "Patient's right to medical information" - which essentially states this right and expressly states the criteria for it's respect în the Romanian health system. In short, the right to information aims to obtain information on the condition and state of health of the patient from those involved in the care process, as well as regarding the limitations of the care process.

It also reiterates the person's right to refuse to be informed, transferring to the medical staff the task of making decisions about the care and therapeutic approaches they receive. The patient retains the right to request and obtain a second medical opinion (art. 11), as well as to receive a summary of the investigations when they are discharged from the hospital, regarding the diagnosis and treatment they have received (art. 12).

"The patient's consent is mandatory in the case of their participation in clinical medical education and scientific research. Persons who are not able to express their will cannot be used for scientific research, except for obtaining the consent of the legal representative and if the research is also done in the interest of the patient" (art. 19).

Informed consent and the respect for the autonomy of research participants

A first approach focuses on the autonomy of the consenting individual and on the intentional adoption of a decision. The decision, once taken, will justify the participation of the decision-maker in the research as a subject, as well as the interventions to which they will be subjected, where appropriate, during the research. From the researcher's perspective, the research is done in good faith when, following the process of obtaining the IC, they have enough elements to justify the belief that they are acting based on the consent of that person (Maclean, 2009).

The process of obtaining IC (Meisel & Roth, 1981) in research involving human subjects, in a manner analogous to obtaining IC for a therapeutic act or a psycho-social intervention, is based on the concept of self-determination, which is called, in the literature on ethics, decisional autonomy. The term refers to the fact that the intellectually competent, adult, and legally responsible individual must be able to make decisions about their own life and health, including those regarding participation as a subject in various researches that may affect their life, health or quality of life to a lesser or greater extent.

The concept of autonomy is defined in the Stanford Encyclopedia of Philosophy as that ability of the individual to live their life according to their own reasons and motivations, based on their own free, unmanipulated and undistorted decisions (Christman, 2020). The autonomous person is, in the Kantian vision, the model of the moral person. Ethical autonomy consists in the self-imposition of the moral law, which must have an universal value. The Kantian categorical imperative proposes autonomy as a fundamental ethical value, being understood as the virtue of acting in accordance with universal law (Guyer, 2004). John Stuart Mill (2014) considers that autonomy is correlated with the exercise of choice and the involvement of reason in the choice process; he correlates autonomy with individuality and originality. Millennial autonomy can be correlated with the self-perception of well-being. The individual acts according to their own definition of well-being, whether rational, instinctive, intuitive, impulsive, or seemingly unjustified. The concept of autonomy and its connotations of self-determination and respect for the person play a central role in the theoretical constructions of applied ethics. Autonomy, understood as negative freedom, refers to the existence of boundaries that limit the intrusion of others into one's own life and one's own decisions.

The competence of the individual to make autonomous decisions is determined by the level of information to which they have access, as well as by the ability to understand the information and to be able to make estimates on the consequences of the decisions taken. The autonomous actions reflect a normative and axiological deliberation on the existing options, both types of deliberation being equally important.

The autonomous person is, in the Kantian vision, the model of the moral person. By virtue of the categorical imperative (Kant, 2010), we must act in such a way as not to harm the freedom and exercise of the autonomy of others, moreover, it is appropriate to promote their autonomous manifestations in terms of their own person and social life (Guyer, 2004). Respect for the person's autonomy therefore requires the researcher to ensure the reality of the IC of the research participants. Moral and decision-making autonomy are defined by the individual's ability to make decisions of moral value for themselves or for others. This capacity is called agency, and the subject who makes the decisions, a moral agent. Decision-making autonomy is complementary to expressive autonomy, the ability of the individual to express their authentic traits in a manner consistent with their own values (Sandu, 2016). Autonomy as authenticity is responsible for the establishing and functioning of the core of human personality. The authentic individual makes decisions in accordance with their own values, sometimes different from those common in society, decisions that may seem irrational and, implicitly, may affect the values perceived by IC researchers.

More specifically, people belonging to certain religious denominations may refuse blood transfusions on the basis of religious belief and authenticity, manifested as expressive autonomy, even if, from a rational point of view, transfusions can be life-saving. In the process of obtaining the IC, all forms of expression of autonomy must be taken into account, including the expressive one, even in cases when a habit or a value of the person precedes their own reason.

The characteristics of informed consent for research

Research involving human subjects should be conducted exclusively on the basis of an opinion from an independent ethics committee (IEC) or an institutional review board (IRB). At least one of these commissions must analyze the research proposal and evaluate it, among other things, in terms of risks for subjects and measures to reduce them, including the procedures for obtaining IC (Gupta, 2013). The three elements of a valid research consent were formulated mainly for clinical research, where the risks that participants assume are usually higher than in psychosocial research, but

which can be extended to any type of research involving human subjects. These are: volunteerism, information disclosure and decision-making capacity.

The voluntary character of the IC is understood as the ability of the individual to appreciate the situation - and make their own judgments - regardless of the opinion of others and in the absence of any form of coercion on what is right or wrong, good or bad, being able to choose what the individual considers it to be the best option in the situation they are in, in line with their own previous values and experiences (Weiss Roberts, 2002). The voluntary nature of the decision may be affected by the person's impaired intellectual capacity, emotional maturity, health, psychological pressure from different persons, including relatives, cultural or religious values, other than those of the investigators or even of the majority of the population, the relations with the medical staff etc. All these risks, which may compromise the voluntary nature of the decision, must be clearly stated in the research proposal and assessed by the Research Ethics Commission or the IRB (Gupta, 2013).

Information disclosure is a gradual process of informing the subject - patient, in the case of clinical trials - about the information they need to know, in a form and language they can understand, about: their health condition, the possibility to participate in research, the therapeutic alternatives to the experimental treatment, the purpose and objectives of the research, its limitations, risks and possible benefits (for the subject, but also for the future development of medicine), possible adverse effects that can be estimated before the start of the research, but also information on the novelty of the clinical approach and, at the same time, the limits of the estimates on the possible adverse effects, the fact that the subject has the right to withdraw from the research at any time and any other information would be necessary în order for the person to be able to make a decision according to one's own judgment, one's own values and life experiences. Incomplete information on the subject is a vice of consent and prejudices the ethical character of the research (Weiss Roberts, 2003). In the case of experimental procedures that include a control group that does not receive the experimental treatment, but only a simulation of the treatment to obtain the placebo effect, the subject should be informed about the possibility of being in this situation. This situation of experiments that include control groups that do not benefit from experimental treatment requires a separate discussion, based on the principle of the patient's right to treatment and the obligation of doctors in the experimental team not to leave the patient without treatment, but this discussion goes beyond this paper.

Decision-making capacity, also called agent capacity, represents the person's ability to understand and appreciate the nature of their health condition, in the case of clinical trials - and the consequences of the decisions they make, how they may affect their health condition, and the ability to formulate and communicate health care decisions (HAV, 2009). The subject must be able to understand the information that is provided to them about their health condition, the nature of the research in which they are required to participate, especially the risks and benefits (Gupta, 20130).

Regarding the ability to make decisions (to consent), a number of problems arise when minors or people unable to consent are among the subjects of the research (Van Hoof et al., 2018), sometimes even due to the condition of health itself (severe mental illness, including senility, dementia, low intelligence or a comatose state) etc., and the consent of relatives is required.

Anita Ho (2008) considers that the emphasis of bioethical research on the acceptance of informed consent neglects the social context of the individual autonomy, which is precisely the environment in which autonomous decisions are made. Anne Donchin (2001) considers that there is a possibility of confusion between the intentions of the subject and those of the people involved in care, due to their concerted action. In some researches, especially in the biomedical field, but not limited to it, the decision to participate or to refuse to participate may be influenced by the social context in which the individual is required to participate in the research, especially when discussing possible innovative therapies with life-saving potential - when the subject decides to participate in order to respect the wishes of those close to them and not to follow their own will. In this case, the expressive autonomy is influenced by the social context, the moral decision being mediated by the social value attributed to the participation in the research.

When participation in a particular research is remunerated, the consent may be vitiated by personal or close financial needs, which incline the decision to participate in the research even if participation would have been refused if it were to be voluntary. In this situation, objections are raised regarding the ethical nature of participation în the research and the reality of the IC.

Conclusions

IC in research is a key element in ensuring the ethical character of any research involving human subjects, whether of a biomedical or psycho-social nature. IC involves three elements: validity, communication of

information and ability to deliberate. Obtaining IC is a dynamic process of ethical reflection, in order to facilitate the expression of the autonomy of the research participant. The process of obtaining the IC must be accompanied by the administrative procedure of completing a consent form, signed by both the research participant and the researcher. If the participant cannot sign - either due to the fact that they are a minor or due to their medical condition - a delegated consent is required, signed by the legal representatives of the subject.

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