Presidenza del Consiglio dei Ministri

COMITATO NAZIONALE
PER LA BIOETICA

SINGLE PATIENT CARE
AND NON-VALIDATED TREATMENTS
(THE SO-CALLED "COMPASSIONATE USE")

ACCOMPANIED BY A JURIDICAL NOTE

27 February 2015

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Presentation

In this document the Committee deals with the issue of therapeutic treatments not validated by regulatory authorities, inserting a further step in the analysis of the different profiles of the right to health, from freedom of care to informed consent, and the doctor-patient relationship.

In particular, the use of theoretically validated products, whose effectiveness and safety for a specific use has not yet been verified, has already been dealt with marginally by the Committee, in 1998, in a brief "reply" to the Ethics Committee of the National Institute for Cancer Research in relation to the so-called "Di Bella case". This was an alternative therapy for the treatment of tumours which required a plurality of "*off-label*" drugs, used for indications, dosages or methods other than those for which they had been authorized. The combination therapy had no scientific basis and was defined as "recourse to impromptu prescription" by the same Law 1998/94 that the legislature had enacted, under the pressure of public opinion and a number of court actions, in order to carry out experimental verification of its claimed therapeutic capacities.

After several years the so-called "Stamina case" has revived the same problems: inadequacy of a scientific basis, public pressure, intervention of judges, impromptu regulatory measures to allow controlled trials. Unlike the "Di Bella case" in the latter matter the combined application of already studied drugs was not called into question, but the very use on individual patients of a not yet approved and largely unknown treatment.

This document only draws inspiration from this incident, for which the judicial process has not yet been completed at the time of writing this opinion. It seems clear that the problem of the administration of non-validated treatments for compassionate use has a specific and independent bioethical relevance for far more complex reasons than those in the Italian "cases", as attested by art. 37 of the Declaration of Helsinki, Article. 83 of EC Regulation no. 726/2004, Article. 13 of the Code of Medical Ethics and the laws of different countries on "treatments on an individual basis", "special access programs," "unproven interventions in clinical practice", "programs of difficult cases", "exceptions for humanitarian use."

The first part of the document describes, therefore, this general reference framework, and then examines the individual profiles from three different points of view: that of the patient, the doctor and the institutions. A very precise choice made by the Committee, who wanted to highlight the variety of needs, experiences and - very often - tensions that arise in these circumstances.

The different perspectives, often do not coincide in the expectations, demands and needs of all parties involved, however, they have allowed us to outline with precision the boundaries within which so-called "compassionate treatments" can be administered, without questioning the consolidated methods of clinical trials, rather, on the contrary, using as a constant reference point and ultimate horizon precisely those regulatory criteria that the medical and scientific community and public institutions share internationally.

The Committee hopes, first of all, that a different expression can be found for "compassionate care", so as not to be confused with legitimate feelings of empathy towards those who are seriously and incurably ill. The alternative proposal is "non-validated treatments for personal and non-repetitive use", in the hope that an international "*consensus conference*" can promote its being used. Access to these treatments should be exceptional, and only in the

absence of validated therapies, in cases of extreme urgency and emergency for patients with a life threatening condition, and such treatments can never be an explicit or surreptitious alternative to clinical experimentation. They must have a reasonable and sound scientific basis: data published in international peer-reviewed journals, with robust scientific evidence at least on animal models and preferably with the results of phase 1 clinical trial. The prescription must be the responsibility of a *panel* of experts, appointed by public health institutions, in conditions of total transparency, absence of conflicts of interest, with publication of both the composition of the products as well as the results of treatment, comprehensive explanation to patients about the potential dangers of treatments non-validated treatments, the cost of drugs borne by the manufacturers and monitoring carried out by public health institutions. Only under these conditions can "compassionate" treatment be considered ethically licit and be included in the general right to health care.

The opinion is supplemented by a detailed legal note, particularly useful given the complexity and fragmented nature of the relevant regulatory framework.

The Working Group was coordinated by Prof. Salvatore Amato and Prof. Assuntina Morresi.

Prof. Lorenzo d'Avack played a central role in the reconsideration of several of the most complex and delicate paragraphs, and in the reworking of the legal note. Prof. Stefano Canestrari, Prof. Carlo Casonato and Dr. Carlo Petrini also contributed to the juridical note.

Prof. Silvio Garattini has revised and made several integrations to the text, which has benefitted from his essential and effective style and scientific expertise.

Notations or written interventions were also received from: Prof. Antonio Da Re, Prof. Paola Frati, Prof. Marianna Gensabella, Prof. Demetrio Neri, Prof. Andrea Nicolussi, and Prof. Grazia Zuffa.

The opinion was approved with 17 votes in favor (Amato, Battaglia, Caltagirone, Canestrari, Casonato, D'Agostino, d' Avack, Da Re, Di Segni, Garattini, Gensabella, Morresi, Nicolussi, Palazzani, Proietti, Sargiacomo, Toraldo) and 2 against (Flamigni and Neri), no abstentions.

Three consultative members (Bernasconi, Conte, Petrini) also expressed a favorable opinion.

Prof. Bruno Dallapiccola, Prof. Lucetta Scaraffia, Prof. Giancarlo Umani Ronchi, Prof. Grazia Zuffa were absent and later forwarded their expressions of approval.

1. Premise

It is often specific cases which determine the bioethics agenda of a country. In Italy the debate on freedom of treatment and on so-called compassionate treatments has taken on particular importance as a result of facts known to the public such as the cases of "Di Bella" and "Stamina". As a preliminary point, the National Committee for Bioethics (henceforth NCB or Committee) clarifies that this document, although it cannot but take account of what happened, it does not intend to enter into the merits of these specific events. We propose, rather, to examine the bioethical aspects related to the cases in question, namely freedom of treatment, informed consent, and so-called compassionate treatment, with the aim of identifying problems and single out, in this particularly sensitive context, criteria and paths to draw to the attention of both institutions and the health professions and, more generally, with regard to public debate.

Within this debate it must be emphasized that medicine, like any other scientific activity, has an essentially paradigmatic (*evidence-based*) nature focused on empirical verifiability (organized scepticism), on shared communication and community and disinterestedness[1].

It is based, therefore, on the ethical pledge to respect for methodologically consolidated rules[2] so that the protection of health is committed to continual review and objective clinical findings for the treatments made available to patients.

Industrialization, namely continuous manufacturing, and generalized and undifferentiated marketing, which concerns the majority of currently available drugs[3] are rigidly bound to compliance with these procedures. Connected to the scientific profile and the economic one of industrial production and marketing is the legal regulation of patents which on the one hand ensures the innovativeness and plausibility of the products used and on the other affects the costs and methods of utilization.

[1] Communalism, universalism, disinterestedness, organized scepticism are the principles set out by Robert K. Merton in the second half of the twentieth century. (Teoria e struttura sociale, Bologna, Il Mulino, 1959).

[2] The NBC has repeatedly stressed these concepts. For example in the document on *Alternative medicines and the problem of informed consent* 18 March 2005 it states significantly that “Scientific medicine, since the adoption of the experimental method, is based on the entirety of knowledge related to the structure and functions of the human body that can be developed through the interaction and integration of various methodologically based disciplines such as physics, chemistry, biology and in particular molecular biology, genetics, physiology, anatomy, general pathology, and psychology. This medicine, which day by day increases its knowledge thanks to the research of many scholars, also deserves to be called scientific for it is able, thanks to a public debate which in principle excludes all sectarianism and every esotericism, to correct itself and modify its concepts and practices with great flexibility, based on the experience of mistakes made and the development of always new paradigms”.

[3] Art.68 of the Legislative Decree. 10 February 2005 n. 30 allows for the so-called Galenic exception that allows the pharmacist, on an occasional basis and for proven therapeutic reasons, to prepare and sell in individual units a drug with a different dosage or different excipient than that put on the market, subject to medical prescription (masterful Galenic preparation) or to make it up directly with or without prescription (Galenic officinal preparation) for a particular patient. These must, in any case, be active ingredients described in the pharmacopoeia of European Union countries or contained in drugs that have been authorized for sale.

Most countries experienced, in recent years, the need to include the administration of drugs or other therapeutic treatments even in the absence of approval of regulatory authorities in various ways:

- *off-label* treatment, which defines the instructions for use, methods or dosages other than those authorized, but for which there are sound scientific basis of efficacy and tolerability;
- compassionate treatment, which defines the use of a drug, not yet authorized, for a single patient (or group of patients).

It is not intended, thereby, to question the traditional criteria for experimentation and use of drugs or therapy, but it allows, exceptionally and on the basis of a medical prescription, to resort to methods of treatment not yet approved by the regulatory authority when the patient is diagnosed with a serious disease, for which there is no validated treatment, or when available treatments have not been effective. Treatments are considered to be effective not only when they lead to a recovery but also when they lead to a better quality of life, relieving suffering and improving the overall condition of the patient. In these cases we are moving, in fact, within the gray area of a scientific validation process that has been started, but has not yet been completed, it is plausible, but not totally verified, with a rationale set forth in the literature of the sector, but not ascertained through the completion of the process that leads to marketing authorization. Situations that find their justification in their appearing to be the only, albeit uncertain, resource remaining in order to try to save a life, prolong it or improve its quality.

To understand the spread of this phenomenon we have to keep in mind the emergence of several factors. Firstly, the rapid evolution of scientific developments creates, at times, an irremovable gap between the normal course of proper experimental verification and the urgency of individual expectations. This phase disparity could condition the choices made by doctors – who are divided between the strict application of established protocols and the desire not to deny any opportunity to those suffering - and affect the way in which the patient and family members deal with the disease, often causing them to pursue any supposed therapeutic promise, seen to be indispensable, given that *evidence-based* medicine is unable to provide answers[4]. Paradoxically, it is the confidence in a science capable of dealing with any disease to fuel the search for a cure at all costs, even beyond the dictates of science itself. In the United States an appropriate expression is used, *quackery products*, which corresponds to our "charlatan", to indicate all "*unproven medications*" widely used, but whose safety and effectiveness is not recognized by the FDA[5].

[4] The International Society for Stem Cell Research in the Guidelines for the Clinical Translation of Stem Cells of 3 December 2008 focuses in particular "about the potential physical, psychological, and financial harm to patients who pursued as unproven stem cell-based" therapies "and the general lack of scientific transparency and professional accountability of those engaged in these activities." Indeed, in recent years a number of companies have arisen which, supported by internet websites and displaying the enthusiastic testimonies of patients, promising cures for incurable diseases according to *evidence-based* medicine. "... Some laboratories promise heaven and earth to desperate patients and their relatives, who undertake sometimes costly and unnecessary 'journeys of hope'. This way of operating is dishonest, although sometimes it is carried out with good intentions, for an essentially consolatory purpose "(E. Boncinelli, *Genetica e guarigione*, Torino, Einaudi, 2014, p. 81 e-book version).

[5] W. S. Pray Ethical, Nonprescription Medications and Self-Care. Ethical, Scientific, and Educational Concerns With Unproven Medications, in "American Journal of Pharmaceutical Education", 70 (6) 2006, pp. 1 ff.

This incongruity burdens even institutions with the difficult balance between the duty to avoid occult, improper or illusory experimentation and sensitivity to the desperation not only of the patients but also of family members, who want to leave no stone unturned to save their loved ones, or at least alleviate their suffering. This discrepancy makes increasingly urgent the problem of giving serious reflection to the nature and deontological limits of scientific information[6].

We can not neglect the fact that we find ourselves faced with one of the many expressions of the need for "personalized medicine" in order to attenuate, under certain conditions and in certain circumstances, the rigid paths of protocol procedures, fundamental in the overall assessment of the effectiveness of drugs and therapies.

Not all situations can be standardized and the relationship between the patient and the doctor can not be traced back to the repetitiveness of similar cases.

No doctor can easily be resigned to the inevitability of what has already happened, in particular before the difference (or the supposed difference) between the attested evaluation of prevailing scientific opinion and the benefits claimed in practice by the patient. It is not easy to ask a patient to give up pursuing even the slightest chance of life or alleged well-being, despite the lack of demonstrated evidence regarding effectiveness at the time of treatment and without there even being any confirmation in consolidated scientific knowledge.

Moreover, the time and costs, that the regulated paths of trials require for permission to market a new drug, cause certain diseases, especially rare ones, not to become the subject of research by pharmaceutical companies. Often the incentive policies towards "orphan drugs" (see. the NBC Opinion 25 November 2011 on *Orphan drugs for persons affected by rare diseases*) are inconclusive due to insufficient economic resources to be implemented. For most of these diseases, therefore, health systems are not able to offer treatment paths or even to treatments for improving the quality of life; in addition there is a lack of suitable experts for these patients, and that diseases like this frequently require the presence of several specialists (ranging from a cardiologist a neurologist, a physiotherapist, to a nutritionist).

An overall picture emerges in which families often are the ones who pull the strings of the treatment paths and healthcare of their loved ones, they become experienced and competent in many aspects of the disease that has affected them, this is especially true if the patient is a child, as unfortunately happens in many cases They are obviously highly motivated families who are fighting against time while waiting for something new from scholars. These families often take an active part in the search for new paths to experiment, thanks to the web that allows direct and easier contact with other patients in the same conditions, as well as with specialists and scientists in that field. Families who therefore ask forcefully and with knowledge of the facts to experiment barely glimpsed or hypothesized paths.

Behind the need to expand some of the limitations normally foreseen for pharmacological and therapeutic experimentation we therefore see the emergence of expectations, hopes, illusions that, in extreme cases in which the patient's life is at stake, fuel strong tensions.

[6] For example in Italy, in the Stamina case, and before that in the Di Bella case, the media had and have a serious responsibility in fuelling expectations and illusions, often aiming more for the pursuit of sensationalism than for accurate information on the quality of the scientific data available.

To what extent it is possible derogate from scientific parameters, and remain within scientific horizons? How far can the wishes of the patient be fulfilled, without creating false illusions? In the perspective of healthcare institutions, to what extent can the "compassionate" approach justify the fact that means and resources are taken from recognized treatments? To what extent can the use of non-validated therapies be left to the unquestionable judgment of the individual doctor, with the possible the backing of a judge? What is the relationship between the right to health and freedom of treatment? Does patient self-determination also involve the risk of experimenting on oneself treatments of unknown harmfulness?[7]

Bioethical culture generally tends to encompass all of these issues through expression full of emotional echoes, "compassionate use"[8] of drugs, derived from the English *compassionate use*: a vague and imprecise formula, reserved for situations very different from each other.[9]

The NBC agrees about the need to amend the term "compassionate care" and replace it with a more effective and more appropriate term to express the concept of " non-validated therapy", which at the same time avoids confusing this particular type of treatment path with a legitimate empathy for patients with severe and fatal illnesses, who are often children.

The Committee suggests using an alternative expression for these cases “non-validated treatments for personal and non-repetitive use", In this formulation the emphasis is placed on the fact that treatments are not yet validated, although one can draw from a significant set of data derived from

[7] These questions have also been reflected in international declarations. Article. 37 of the Declaration of Helsinki (updated in October 2013) provides for the possibility of "unproven interventions in clinical practice." It allows the use, under the responsibility of the doctor and with the consent of the patient or his legal representative, of "an unproven intervention," when there are no proven treatments or other known interventions have proved ineffective, and after seeking expert opinion on the subject. The doctor must be convinced that this drug could "constitute a hope to save the life, restore the physical integrity or alleviate the suffering of the patient." The regulation adds that "This action should then be made as an object of study, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and made publicly available when appropriate." In one of the many drafts of the Universal Declaration of Unesco "on Bioethics and Human Rights", art. 16 of *Scientific and Rational Method*, after pointing out that every decision and practice should be based on the best scientific information available, stressed that (v) “be considered individually, allowing for the possibility of exceptions to general rules and practices”. The article was then removed from the final version, but it is the sign of a debate within the international community itself.

[8] In international literature there are also "treatments on a named-patient basis" and “special access programs”, "Unproven interventions in clinical practice", "temporary authorizations for use", "programs on difficult cases", "exceptions for humanitarian use," "non-repetitive use of advanced therapies." Each of these definitions reflects a different possible interpretation of a phenomenon that is as difficult to curb as it is to define within univocal patterns. Even our legislation utilizes a wide range for variations in terminology which now reflect the tensions of the moment - "use of extemporaneous prescription" (Di Bella therapy) - currently affect various aspects of the phenomenon: "use of drugs for indications other than those authorized", "use of drugs outside of clinical trials", "prescriptions for indications not provided for by the technical information or not yet authorized for the market." The attached note explains in detail the use of treatments and medication for "compassionate use", within the current legal framework.

[9] Sometimes it is suggested to reserve the term "compassionate use" only in situations where the administration of not yet commercialized drugs occurs for groups of patients and under the control of an institutionally appointed body responsible for scientific experimentation, using instead "*Treatment on a named -patient basis* "or" *Special access programs* "(SAPs), to describe the prescription of *off-label* drugs or drugs not yet authorized for individual patients and under the responsibility of individual medical institutions.

international scientific literature and reasonable scientific evidence to justify the assumption that such treatments can be validated (but of course there is no certainty that this will then actually occur). Since the NBC is aware of the difficulty of replacing a synthetic expression and corresponding to a literal translation of the original definition in the English language "*compassionate use*", it suggests the creation of an International "*consensus conference*" to reflect on this specific issue.

Precisely because of the difficulties mentioned above, and so as to avoid misunderstandings, the adjective "compassionate" will still be used in the rest of the document.

2. Bioethical profile

Even the terminological difficulties are the inevitable consequence of the extreme variety of situations before which we stand: the right to health is understood in an increasingly broader sense so that, in addition to including the quality of life, it extends to the expectations and life expectancy stretching to, in extreme cases of incurable diseases, a need for "compassion" that encompasses everything that can possibly be done to "To alleviate not only physical injury but, if you will, also the patient's existential injury"[10], in order to be able to at least alleviate his conditions, while not being able to hope for any recovery. The crucial point of this placement of health within the protection of the spheres of freedom is constituted by the problem of freedom of treatment.

Freedom of treatment is an aspect of the right to health, but is not the main content of this right, because healthcare assistance requires regulation and coordination of functions and services, which can not be entrusted entirely to individual choice. The prescription of a drug within the National Health Service (NHS) always involves monitoring its mode of administration and an evaluation on justice in the allocation of resources. A complex process that moves from each individual, but which goes much further, involving the entire health care organization.

It is different if we prescind from the NHS but the prescription takes place equally under medical supervision, as in some forms of "alternative medicine" on which the NBC has expressed itself in the previously quoted opinion *on Alternative medicines and the problem of informed consent,* with reference to "practices whose effectiveness have not been established by the criteria adopted in scientific medicine" (an expression similar to that of compassionate treatments, considering that in these efficacy is not "proven", despite being "ascertainable"). The NBC has reiterated, in this document, the general principle by which, notwithstanding the responsibility of the doctor in the

[10] "The principle that the right to health has in our legal system is extracted from these considerations, a certainly broader dimension than that which merely derives from the right to treatment or healthcare in the traditional sense of appropriate therapeutic measures to wipe out the disease or to stop its evolution. On the contrary, the necessary reference to the protection of human dignity, allows for consideration that the health conditions the subject of constitutional provision coincide not only with the preparing of means to heal the affected person but also with whatever else may be used to alleviate the not only the patient's physical injury, but if you will, also the existential one, at least as concerns whatever may be of real utility in alleviating the functional limitations albeit without any appreciable results regarding the possible regression of the disease" (Court of Cassation, sez. Civ. Work, 18 June 2012, n. 9969).

administration of any therapeutic treatment, at the express and conscious request of the patient and in specific cases, the administration of scientifically non-validated products is justified, provided that they are not charged to the NHS and however always as a last resort or in the absence of validated alternatives and risks being ascertained for the patient[11]

In general, if interventions not approved in clinical practice are requested, the argument often put forward is that it is one aspect of the freedom of treatment, this "claim" or "expected" aspect, expresses the demand, by the patient, to receive treatment not yet validated by the scientific community, but for which the available data portends the possibility that it may be of benefit. In other words, faced with the declared powerlessness of *evidence-based* medicine, the patient raises the question his being "free" to look elsewhere for a cure at all cost, thus giving priority to his autonomy.

The other side of the freedom of treatment is the refusal of medical treatment, which has been dealt with in a previous NBC document (*Conscious refusal and renunciation of healthcare in the patient-doctor relationship* 24 October 2008), examining in particular the issue of the right to refuse treatment, in its broadest sense to choose the method of treatment, or not to be treated at all, and the role of the doctor If during renunciation or the refusal of treatment the active role of the doctor were to be requested. In that opinion, the NBC highlighted that "in current medical ethics, informed consent has taken on a key role, allowing full valorisation of the choices made by the competent patient, according to the principle of autonomy", and reiterated that: "when, in the case of a competent patient in conditions of dependence, the renunciation of treatment requires, in order to be satisfied, the active behaviour of a doctor, the doctor's right to abstain from behaviour deemed contrary to his conception of ethics and professionalism is recognized. A large majority of the NBC considered that patients have in any case the right to attain alternatively the fulfilment of their request for the interruption of treatment, even in consideration of the possible abstention of the doctor or medical *team*."

In understanding the problem of compassionate treatment some misunderstanding may arise precisely if one proceeds in the perspective of a general statement of freedom of treatment (or generic therapeutic self-determination). Instead, one must take into account certain distinctions. For example, the refusing of medical treatment is not based on the principle of freedom in a general sense, but on the protection of the physical and mental freedom of the individual whose bodily dimension must be respected. The request for special treatment is, however, a request for medical intervention, which, as such, operates according to the criteria of professional appropriateness and conscience. The dividing line, although controversial and problematic, between appropriate and inappropriate treatments defines medical practice and takes on a very particular importance precisely when the treatment requested is not in compliance with normal medical and scientific standards. Consequently, defining the dividing line between permissible and impermissible

[11] The Supreme Court (Work sect., 20 May 4 September 2014, n. 18676) reiterated that the right to health is not susceptible to weakening. The patient has, therefore, a right to obtain timely care free of charge, even if it is not recognized by the National Health Service. However, these services must respect the principles of "appropriateness" and effectiveness of the drug or therapy within the parameters set by law. A careful comparison is necessary "between the positive results of health care and the possible negative effects of the therapy itself on the living condition of the patient."

compassionate treatments is necessary not only for the sustainability of the NHS, an already decisive issue at least in terms of the availability of resources, but also for the autonomy and professional responsibility of those working in the healthcare sector. It then becomes a crucial problem whether, in the event of a fatal diagnosis and the absence of validated therapies, both for treatment and improvement of the quality of life, the "best interests" of the patient can be configured by a course of treatment not validated according to the shared criteria of the scientific community, which therefore could not even have been verified in terms of harmfulness to the actual patient. The NBC intends to analyze this problem from three points of view - that of the patient, the doctor, and the institutions – in order to try to highlight the variety of tensions that arise within the different standpoints that do not always fully coincide.

3. On the side of the patient

1. The patient's right to treatment and therefore to the protection of health, is first and foremost, the right to receive treatment approved after rigorous experimentation according to the methodological and ethical criteria shared by the scientific community and regulated by the legal system. In this context the NHS in the dispensing of medicines and medical treatment carries out a dual role of recognition of compliance with the parameters set by the law and monitoring of the adequacy of expenditure in relation to individual needs and the interests of the community. This paragraph deals with the legal aspect of the conduct of conscious and properly informed patients, who at their own responsibility undergo treatment that has not been validated. The following paragraphs examine the issue of the right to obtain this treatment on the NHS and the role of the doctor.

The basic rule is that the administering of non-validated treatments should take place only as a well motivated and strictly monitored exception, their sole raison d'être occurs when faced with a life threatening situation or the particularly serious nature of a disease, there being no recognised effective alternative for treatment and improvement of the quality of life of the patient in order to prevent deterioration.

In the context of compassionate care the patient's request to use a drug that has not been registered and to evade the authorization procedure established by the regulatory authorities, is characterized by the fact that the procedure has not been completed or even begun on human beings. It is therefore a matter of waiting for the patients[12] undoubtedly, in general it is wrong to think of "saving

[12] See the case known as "Lorenzo's Oil", where the parents themselves obtained the substances to be administered to the child and where it is clearly evident that time is life for the patient: *"Suddenly it was clear as day: we were running on parallel but completely different tracks, as if research for science was one thing, but our fight for life was another. As if we were in the real world and they were in their world of abstract solutions, and the two worlds, separated by a thick sheet of glass, were unable to communicate. During the very days of the conference Lorenzo had stopped walking completely, he no longer spoke and had started having big problems swallowing saliva, which had to be sucked through a tube of plastic similar to those used by dentists. It kept going through my head that phrase used by Rizzo: "Maybe triglyceride would be suitable, but I would not know where to find it ..." A surge of anger took hold of me and took the form of a bitter question: Were they trying to win the Nobel Prize while I was witnessing the death of my son? (pp. 62, 63) This position is sometimes misunderstood and seen as controversial. Some have accused me of wanting to hurry to the progress of science;*

time" by replacing the rigor of the *trials* of the authorization procedures with the anecdotal attempts of compassionate use. Moreover, in the context of these events there is no intention to replace rigorous scientific experiments with compassionate use, but rather to complement new attempts for treatment to due experimentation. These attempts should not be conceived as being “outside" of scientific experimentation, but "alongside " it, as anecdotal cases which however do not interfere with the trials, but accompany them not usually but only in exceptional cases and with carefully defined methods.

We can configure at least two situations. The first, in which the patient might have access to a treatment path for which experimentation on humans has already begun, and for which at least phase I has been completed. The second, in which no trials on human beings have begun.

In the first case, that is, with evidence of no harmfulness, the patient could have access to "compassionate care". It is therefore possible that in the course of a clinical trial the drug, within highly specific conditions, may be utilized prior to being approved as a compassionate treatment. This would be a form of early access, extended to the sick in exceptional circumstances still to be accurately established , and which should however take place in a strictly controlled manner, both by the relevant authorities through the treating physicians, and also possibly by patient associations. In this way it could give rise more easily to a virtuous circle of information regarding the entire community of patients suffering from the same disease. An early access, but with established criteria[13]: the purpose would be to speed up access for patients who do not have an alternative, when the trial has already concluded Phase I and therefore there has been recognition of drug tolerability so as to justify continuation.

The most problematic situation is undoubtedly the second, which usually occurs for rare diseases, for which there is no regular experimentation in progress or reasonably foreseeable in the near future, because it is too costly for pharmaceutical companies, considering the small number of sufferers. The problem arises when the patient in this situation consciously requests a therapy for which the absence of harmfulness is unknown and the patient who is not able to access the therapy autonomously, requires medical intervention.

The most common case can be, for example, the one concerning rare diseases for which there is reviewed scientific literature, but it is limited to some experiments on animals (see the already cited case "Lorenzo’s Oil"); or, as is increasingly occurring with the “journeys of hope” for cellular therapies in the case of fatal diseases: the patient is not able to independently access this path even when, in autologous transplantation, the patient actually personally provides the biological material, because the intervention of lab technicians and doctors are needed[14].

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science, they said, should follow its own pace. For me it was nonsense. But I discovered that it is not easy to change the mindset that has always existed in the field of science, often closed to the outside world. We could not accept the idea of a research which adopted the slow pace scientists were accustomed to. " (A. Odone, *Lorenzo's Oil*. A love story, Milan, 2011, p. 91).

[13] As required by the Ministerial Decree of 2003 with expenses charged to the manufacturer of the drug. The Decree currently limits recourse to the existence of a "life-threatening" condition and with phase III drugs.

[14] We do not go into the merits of the specific problems of advanced therapies i.e. the treatments involving the use of material based on cells and tissues, for which the EMA applies the same safety criteria applied for pharmaceutical products. It is a complex issue that has a significant role in the case of "compassionate care", but it requires a specific analysis which may be in future the subject of a separate NBC opinion.

In this regard, what happened with the so called "Ebola case" is of great interest, the disease in itself though rare encompasses the added danger of being contagious and rapidly spreading, which can turn into an epidemic with a high mortality rate, this makes it even more urgent to attempt to find a solution, in the interests of the individual, as well as the community[15]

Whichever way one perceives the matter of "compassionate treatment" within or outside of trials, questions arise to which it is not easy to give a definite answer.

Is it licit to prohibit a treatment in the name of "safety" when the only "certainty" the patient has is that of death, in the short term? And what about when the risk is not only personal, for an individual patient, but the health of entire communities is at stake, as in the case of contagious diseases with high mortality? Is this prohibition licit when the patient has given consent, aware of the fact that the treatment is very high risk? To what extent is the patient free to dispose of his body, when the alternative is certain death, considering that from this act no commercial profit is derived? Would it make sense to call into question the "precautionary principle", in relation to the conditions of uncertainty and risks, when any adverse events might occur when the patient is, presumably, no longer alive?

A hypothesis to be considered is that in which the patient consciously requests therapy which was not yet been through phase I of clinical trials, but he is not able to access it autonomously, and requires medical intervention. In this specific situation, according to the principle of autonomy, in order to invoke the right to "compassionate treatment" various scientific evidence should be found regarding the reasonable probability that the product can be beneficial, and that the risk is proportional to the possible benefits. The "reasonableness" should concern the minimum level required of available scientific evidence in this regard, without which the same treatment would be unreasonable and therefore unacceptable. This level should define both the type of information present in literature, as well as the quality of the scientific literature itself.

There should be available at least robust and abundant evidence of it working from experiments conducted on animals[16] and the scientific journals in question should be internationally distributed and *peer review*, that is, whose articles are subject to evaluation by means of review by experts of equal expertise.

Moreover, conflicts of interest on the part of those taking responsibility for the prescription should surely be excluded, this should not be a single doctor, but rather a panel of experts specified by the NHS authorities, which in a short time and in any case compatibly with the situation of the patient who explicitly so requests, is capable of expressing their views to this regard, on the basis of available scientific evidence (as in the case of the WHO on the Ebola epidemic). Precisely in cases like this, when it comes to rare diseases, studied by few specialists, for which assessments of possible treatment not yet undergoing trials are based on highly specialized scientific literature, is it likely that a single

[15] However, the spread of the contagion may not be sufficient to allow compassionate care only in these circumstances and therefore, for these patients, become an advantage. If we consider the point of view of the person affected by a rare disease, with a high mortality rate even though not contagious, the absence of the risk of it spreading paradoxically would deprive these patients of opportunities which others have to attempt a cure.

[16] In relevant animal models, and in particular in non-human primates, for example, specifically the statement of the WHO regarding Ebola.

doctor (and even more so in the case of a general attending practitioner), will be incapable of judging the situation properly.

An illustrative example would be the use of non- validated drugs recently authorized during of the abovementioned spread of the Ebola virus. The exceptional nature of the circumstances led the WHO, last August, to consider positively the use of treatments to combat Ebola, that were not validated on humans but successfully tested on animals; in this regard the WHO spoke explicitly of "*compassionate use (access to an unapproved drug outside of a clinical trial).*" A *panel* of experts concluded unanimously that "it would be acceptable on ethical and evidential grounds to use as potential or preventive treatments unregistered therapies that have shown promising results in the laboratory and in animal models, but which have not yet been evaluated for effectiveness and safety in humans, provided that certain conditions are met. When formulating these findings, the members of the panel are aware of moving away from the well established and historically developed system of regulation and *governance* of therapies and interventions[17]. The document describes in detail the exceptional nature of the situation, and lists key considerations for the use of non-validated therapies, stating that "in the exceptional situation of the current Ebola outbreak, there is an ethical imperative to offer the experimental interventions available have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing the disease" provided that the specific conditions defined by the *panel* itself are met.

The CNB does not intend to go into the specific merits of the aforementioned experimentation, but rather the methods of "*governance*" of this emergency: authoritative public institutions, recognized by the scientific community and international politics, such as the WHO, facing a situation of an exceptional nature, have identified an equally exceptional path, outside of the ones currently regulated according to criteria of transparency and appropriateness from the scientific point of view. In this sense, the NBC refers to the "Ebola case" as an example of health *governance*, regardless of the outcome of the specific trials underway.

When these conditions occur and anticipating future observations[18], the Committee intends to embrace the hypothesis that it is possible to authorize non-validated treatments (that are validatable)under the supervision of specifically authorized medical personnel, even beyond the limits currently envisaged by DM May 8, 2003, with all the precautions that will be subsequently mentioned. Within these particular cases we could therefore speak of the "Ebola case" as a means of access to compassionate use in analogy to the criteria and procedures designed by the WHO in this circumstance[19].

More critical is the indispensable requirement in any medical treatment of informed consent.

How "informed" can consent to treatment be, if we do not know the scientific assumptions, methods of administration, the possible side effects? Informed consent is not only the assent to a particular therapy, neither is it an act of will, as such, binding on the doctor; it is rather the outcome of a process of engagement and learning based on information that should as complete as

[17] http://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/

[18] Cf. *ultra*, p. 24.

[19] Clearly in the above example of early access the assessment is less problematic because of the ascertained absence of harmfulness.

possible. The particular connotation ethical, deontological and juridical connotation of information/communication should receive even greater attention, in delicate situations such as compassionate use. The profile information constitutes for the patient a genuine right whereas for the doctor it serves as a duty. Consequently, the obligation for the doctor to provide clear and received comprehensive information and the utmost attention must be paid to this moment of empathy when the effectiveness of the treatment and its harmfulness is not very evident. The shared objective is to enable the patient to make an informed decision that is appropriate to the situation and his expectations of health, with a broad connotation given to the latter, remaining open both at the time of "*treatment*" and "*care*". The utmost transparency and clarity is required of the doctor especially if the possible side effects and potential harmful effects of the therapy are unknown, so as to allow patients to exercise their autonomy, with a view to balancing the desired effects and the quality of life remaining after truly thoughtful consideration.

Faced with treatments that have not yet been sufficiently tested, informed consent, even with all the limitations due to the peculiarities of the situation, can only be in part a declaration of personal acceptance of risk, considered valid only if expressed after encountering physicians who agree on the reasonableness of the request.

The absence of validated treatments can not, however, make consent to an alleged cure which lacks any rational justification legitimate, it being founded only on the will of the patient. Otherwise there is the risk of transforming patients from victims to be rescued into guinea pigs to be exploited. It is easy to move from compassion to illusion, only to endorse practices which have no justification in our legal system and no scientific and bioethical foundation.

2. When severe fatal pathologies affect children, as is the case with many rare diseases, diagnosed in infants or babies a few months or few years old, the issue of "compassionate treatment" takes on an absolutely dramatic importance. Feelings of helplessness and the will to hope against all evidence often go hand in hand, fuelling each other. One is ready to do anything faced with the innocent suffering of one's own child, and it is no coincidence that the "Stamina issue" has taken on stronger tones with regard to rare diseases in young children.

But responding to the endless pain of these circumstances with illusive and deceptive therapies is the greatest cruelty that can be inflicted on families already so sorely tried, and it is the very opposite of "compassion".

What has been said so far about the issue in question can be extended to patients who are minors, with some clarifications regarding prescription and informed consent. The panel of experts, eventually called upon to rule on prescribing "compassionate treatment" or not to minors, should necessarily include neonatologists or pediatricians with proven experience for the age group of the children involved in such treatments. Among the criteria for prescription it is essential, in fact, take into account the huge differences in levels of development among the people within the category of "minors".

With regard to informed consent, by parents or legal guardians, as generally occurs in the context of health care, it must involve children proportionally to their age, maturity and awareness of the situation in which they find themselves.

Nevertheless the problem of how to give voice to the child is a delicate one, without adding to the trauma of illness the trauma of information which becomes

more tragic the clearer and more complete it is. Appropriately in the document on *Information and Consent to Medical Acts* June 20, 1992, the Committee devoted a special section to the "informed consent in pediatrics", moving from the idea that " ...the conception of informed consent in pediatrics is different, due to the undoubted impression received from the knowledge and perception of reality in children and adolescents, their development in the environment, the way they belong to the world, the way of belonging of their parents, and the capting of their verbal and analogical communications, expectations, requests and proposals." To ask, at such a delicate moment of development, to decide on their own life can have a profound effect on their trust in the ability of "grown-ups" to provide aid and assistance[20] We will never have the certainty that the search for the opinion of the child does not end up unwittingly and indirectly, in determining the loss of all illusion, but we will never even be sure that by doing the opposite, relegating the child to ignorance and incapacity, that we are operating in the best way to guarantee his good. The subsequent NBC document *Bioethics with childhood* 22 January 1994 states, for example, that "children with a chronic illness, duly informed about the characteristics and long-term treatment, demonstrate their capacity to accurately carry out requirements. It has been demonstrated in children with asthma that providing adequate information decreases the number of medical consultations and the frequency of hospitalization."

Therefore, we can not ignore, the will of the child, neither even the existential sacrifice that is entailed by the loss of illusions and hopes. The principle of autonomy demands the recognition of the dignity of the adult, but that of beneficence could prompt to delay entry into the adult world, constrained by illness and suffering. How should a correct biogiuridical classification of the will of the minor be given? One could speak of a compulsory, but not binding opinion; or of a weak autonomy only "potentially decisive"; or a non-binding opinion *prima facie*, that becomes binding once assumed.

It is fundamental, in this regard that the child and his family members are not left alone. The role of associations is of particular importance, tending to bring closer both the families taking charge of their loved ones and the young patients themselves. This associationism comes from the desire, if not the necessity, to share a painful experience, as well as the skills so laboriously and painfully acquired "in the field". Very often it is this sharing of common experiences that is the best antidote to the spread of illusory promises of therapies that are decisive or at least "miraculous" on one hand, and on the other it is a unique opportunity for the diffusion of good practices even "compassionate" ones.

3. In these situations the "right to hope"[21] has often been invoked. But is there such a right?

[20] Children are much more fragile than adults, less able to be resigned to the advance of illness, more frightened by and biological and corporeal situations , which they often do not fully understand the origin and meaning " (P. Cendon, *Cellule staminali somministrate ai bambini sofferenti di gravi malattie neurologiche,* in ”Minorigiustizia”, 2013-2, p. 241).

[21] A Right invoked in several judgments in our country especially in the case of Stamina. In the United States it is invoked as the "*right to try*". Significantly in several states (Colorado, Louisiana, Missouri, Michigan, Arizona) there have been specific laws enacted regarding this "right to try", to allow quick access to the drugs being tested, without being subject to the restrictions of *the Food and Drug Administration*.

In this experience of pain and suffering the sick patient can find strength and support in the daily hope of healing or at least of not seeing his condition deteriorate. He may also have faith in the advancement of scientific research and the experimentation of new treatments which may be of benefit to his health and the health of other patients in the same conditions. In extreme cases hope may go as far as the taking of a risk, on the basis of a positive personal attitude, the will to pursue a remote possibility, on the basis of the conviction that a solution may exist, for example by following non-validated or experimented paths.

The Committee observes, faced with such a human and respectable sentiment(that nevertheless it can not be interpreted as a “right”), and the only way that institutions have to guarantee “hope” for the patient to find a therapeutic solution is the control of “how” they are treated and over “those who they place their trust in”

The compassionate use of a drug must be the exceptional situation that leaves space for a gleam of hope, but which excludes any space for speculations that are fuelled by illusions.[22] It is the same Constitutional Court (n. 185/1998) to recall, regarding special and temporary authorization for the therapeutic use of drugs outside of trials, that in cases of extreme therapeutic requirements, that are urgent and without alternative answers that the expectations comprised in the minimum content of the right to health care undoubtedly arise. At the same time it appealed to distinguishing between hope in "any treatment deemed effective" and the therapeutic hope based on strict objective parameters (drugs under clinical trial and a special temporary authorization for therapeutic use), and subjective parameters (the doctor considers under his own personal responsibility, and on the basis of objective elements, that there are no valid therapeutic alternatives using already validated medicines or treatments for these diseases) and temporal parameters (at such time it is not possible to have scientifically reliable data).

It is crucial that doctors, as legislators and judges, in an attempt to give voice to the requests of those suffering, never lose sight of the fact that therapeutic hope must be based on reliable scientific bases.

4. On the side of the Institutions

The term “institutions” refers to all those involved, in various capacities, in the process of the "government" of the administration of drugs and have the responsibility of ensuring quality and safety of clinical treatments: National Health Service, Ministry of Health, National Institute of Health, AIFA, hospital facilities, ethics committees, doctors and judges.

The administrative and juridical regime of assessment of the effectiveness of a drug or a treatment responds to requirements of social security. Requirements imposed to guarantee both the health of the citizen as well as the

[22] As emphasized by the *International Society for Stem Cell Research*, in the *Guidelines for the Clinical Translation of Stem Cells* 2008, one must bear in mind the difference between the illegal marketing of interventions with stem cells not adequately tested and the legitimate attempts at medical innovation outside the formal context of clinical trials. It therefore invites the regulatory authorities of various countries to prevent exploitation of the credulity of patients, closing the clinics in which this fraudulent activity takes place and taking disciplinary action against the doctors involved.

proper functioning of the public administration. It should also be borne in mind that the administration of drugs and therapies requires a delicate balance in the allocation of resources. With the consequence that, from the point of view of the institutions, until the administrative *iter* governing marketing has been completed, the drug does not constitute a valid therapeutic response to the disease and therefore does not come under the right to health.

Derogation from this principle, the "'compassionate use" of drugs implies a different involvement of the various levels of "*governance*". We have a kind of reversal of the decision-making process that is no longer directed from above, from the decisions taken by the political and administrative authorities, but it moves from below, from the immediate and undeferrable interest of the patient, certified by the doctor's prescription, to then go up to the other steps of the public and private institutions: from the pharmaceutical companies that must provide the drug to the hospital facilities that must administer it.

The judge intervenes, in turn, when a conflict between the different levels is determined. The delicate point is the existence of efficient connecting bodies, both scientific and ethical, which can ensure, in a short time and with adequate information, a proper level of interpenetration between individual choices and general interests, avoiding (as in the case of the "Stamina method "and even earlier with the case of the "Di Bella therapy") that systematic and constant recourse to the courts that has determined the end of each matter in itself, without any guarantee of respect for the principle of equality and evaluation of general interests . The constitutional principle of the division of power and the subjection of the judge to the law imposes, even before the most dramatic situations, to operate in compliance with established scientific parameters, without confusing the expectation of relief and the desperate search for a remedy with the right to health.

This dual mode of developing the decision-making process, "from the top" or the "bottom", reflects the diversity of requirements that are involved, both fundamental in the configuration of the right to health. The first requirement regards the monitoring of the scientific reliability and the procedural rigor of the trial in order to ensure a standardized and generalized fruition of the drugs. We have a preliminary assessment of the benefit-cost ratio entrusted entirely to the regulatory authorities. The second requirement relates to the duty not to foreclose the prospect of survival or improving the quality of life solely to the person who is suffering. In this case the evaluation of the ratio between benefits and costs lies essentially with the patient and the attending doctor, with individual effects that can only be evaluated *ex post*.

These two requirements are different. One can not be assessed exclusively with the canons of the other, neither can one even be implemented, altering the structure of the other. The task of institutions is precisely that of trying to make them as compatible as possible.

Therefore the role of ethics committees is particularly delicate and recalled by the DM December 5, 2006 in relation with the art. 6 of Decree 211/2003 on the testing of medicines for clinical use. The judgments given on the " Stamina case", for example, configure on the role of ethics committees four different hypotheses in relation to a far from clear regulatory framework:

a) The committee's opinion is irrelevant because it can not affect the doctor-patient relationship and the patient’s freedom of healthcare.

b) The opinion must be requested, but it is not binding for the doctor

c) It is necessary and binding, but it is sufficient that it has been provided on a similar case.

d) It is necessary and binding and must be expressed case by case.

The NBC stated in the Note on 16 January 1998 regarding the cancer therapy given by Prof. Di Bella, that "if an ethics committee structure is requested to give an opinion, which does not imply an organic experimentation according to current regulations, but solely a judgment of ethicality or otherwise of an unusual or alternative therapy, practiced on a single patient, the committee's opinion is however not binding because it is up to each individual physician, the professional responsibility for decisions on innovative and alternative therapies can not be delegated, it can be broadly favourable, provided that there is, in that particular case, on the one hand the gravity of the patient's conditions, and on the other the uselessness of other established therapies, such as to constitute a real state of necessity that can justify any reasonable attempt at a therapeutic alternative".

As can be seen, the regulatory gap, in this case, is particularly evident. comprehensive legislation is needed which clearly defines the role of ethics committees and their relationship, when it comes to non-validated treatments for personal use and not repeated treatment, with the autonomy of medical choices.

Particularly delicate, in these cases is, the recourse to procedures for convening and emergency decision where the regulatory provision for deliberations *on line* is increasingly frequent, these do not allow for adequate discussion and effective weighting of the plausibility of the treatment, the sufficiency of scientific information, the relationship between risks and benefits.

It also raises the issue of whether or not the patient is entitled to non-validated treatment under the NHS and reimbursement of costs. As is known, in Italy the reimbursement of the cost of medicines and medical treatment is provided to patients under a system which divides into different classes, A (paid by the NHS), C (cost is borne by the patient) and H (attributable to the hospital), where usually the total reimbursement is approved for essential medicines with proven efficacy intended for chronic conditions. Even the Constitutional Court (n. 274/2014) in a decision on the Stamina case explained that "the promotion of a clinical trial to test the efficacy and exclude harmful side effects of a new drug does not allow as a rule, to charge in advance to public facilities the administration of the drug itself: and this is so for obvious reasons of health protection, in addition to the requirement of proper use and allocation of funds and resources at the disposal of the NHS." Nevertheless, the legislator has on more than one occasion mitigated the objective rigidity of the system not excluding charging to the NHS the administering of drugs not belonging to class A when they are essential for the treatment of serious diseases in a prolonged therapy. Not yet excluded on the NHS are the medicines already authorized in other States, but not in our own country, or that are not authorized yet, but undergoing experimentation, i.e. *off label* treatments, on the condition that in all these cases there is no other valid therapeutic alternative.

This is an exception that has been admonished many times by jurisprudence regarding the abovementioned cases[23]. However, these services must respect the principles of "suitability" of the drug or therapy within the parameters laid down by law, and effectiveness which requires "necessarily a

[23] C.f. among others Cass. no. 1665/2000; Cass. no. 2034/2000; Cass. no. 18676/2014.

comparison of the positive outcomes of health care and the possible negative repercussions of the therapy itself on the living conditions of the patient."[24]

As concerns, "compassionate" treatments and drugs there is no clear regulatory framework that ensures, on the one hand, to the doctor at his discretion the legitimacy to prescribe a non-validated treatment (although judged appropriate according to best knowledge and belief) and, on the other hand, the adhesion of the State with the consequent acceptance of its financial costs.

A hypothesis that the committee endorses is the one indicated above as "the Ebola case." The NHS may allow the patient, even beyond the limits currently envisaged by Ministerial Decree 8 May 2003, to receive non-validated treatment, under the supervision of specifically authorized medical personnel, in exceptional cases and under strict conditions: the absence of alternative therapy; urgency and emergency that place the patient in danger of death or rapidly progressive serious disease; authorization and monitoring entrusted to a panel of experts or institutional committee ; real-time publication of all the results.

In the case of a patient admitted to an accredited state or private facility the drugs should be charged to the NHS seeing as the costs on admission are inclusive of the pharmaceutical treatment carried out (see, ex. p. 32 Legal appendix: e.g. L. 94/1998); however in these cases given the high cost, it would be appropriate if this was borne by the manufacturer of the drug, who receives, in any case, a benefit from the information that is acquired.

A delicate aspect arises when the recruitment of single patients involved in compassionate use, interferes with the protocols of the actual *trials*: in this case, in the NBC's opinion, the anecdotal outcomes must be presented separately from the final results of the clinical trials authorised in compliance with standard procedure.

In order to avoid creating easy illusions, to prevent running into speculation and to strengthen the support network and support to patients and family members, the NBC considers it the bioethical duty of public health institutions to encourage the spread of clear scientific information on sites accredited sites by authoritative bodies or research institutions[25].

5. On the side of the doctor

We refer in this section to "doctor" in the singular, giving this word also the meaning of "panel of experts" in the terms illustrated above. As can be seen from what has been observed previously, the doctor performs the most delicate role, because he is as much the representative of the institutions and the guarantor of the proper application of treatment protocols as the participant to whom the suffering and despair of the patient and his family, he experiences, often almost with a sense of guilt, the full weight of helplessness, of not being able to provide adequate relief. The dramatic situation may result in mutual pressure, between patient and doctor: the one expects a remedy at any cost and the other tends to provide it in every way. Torn between resignation that is

[24] Cass. no. 18676/20014

[25] Recommendation already present in Opinion: Ethics, health and new information technologies, 2006.

difficult to accept and compassion which is difficult to achieve. the doctor has the duty to advise the best treatment "available", but in the absence of known remedies the concept of "availability" becomes vague, extending to the probable and possible. Does it even extend to what is supposed? What is the threshold beyond which it is not permissible to go?

The response should be found in the difficult relationship between the maximum benefit hoped for and the least harm foreseeable. In this weighting a part of jurisprudence holds that even a "mild" improvement or even only the hope of an improvement could have its own weight. From the logical point of view the opposite argument is just as plausible: if we are not sure that a drug "does some good," neither can we say that it does no "harm"; if the benefit is not predictable, neither is the foreseeable damage.

It is not possible to expect to circumscribe in clean way the margin of appreciation left to the doctor in the assessment of these critical situations.

If the doctor can not become a seller of illusions or a hired conscience endorsing any request, neither can he ignore, in the primary interest of the health of the patient, the innovative therapeutic prospects that seem plausible to his professional conscience.

Therefore, differences can emerge both in the assessment of the performance of individual doctors as well as in the relationship between the doctor who prescribes the treatment and the doctor who is called upon to implement it. The NBC notes that, in this case, the doctor called upon to administer a therapy, prescribed by others, for "compassionate" reasons, has not only the right but also the duty not to carry it out, if he does not believe in its effectiveness or if he believes that it may be absolutely dangerous. The right to professional autonomy and the duty to respect, to best knowledge and belief, the dictates of *lex artis* prevail over the possible need to ensure therapeutic continuity. This is not a case of conscientious objection, because we are not dealing with a conflict of values or different visions of life, but the respect of those fundamental principles that form the basis of the medical profession.

Although an unfathomable margin left to personal evaluation, can not be eliminated, regulations that provide clear guidance to the doctor are essential, as part of a weighted evaluation of the relationship between the social profiles of the right to health care and the subjective margins of freedom of treatment, a valid support in the taking of responsibility. The recent events in Italy highlight how difficult it is, within a plurality of heterogeneous regulations enacted at different times and for different purposes, to have a correct assessment of the many possible situations within the recourse to innovative practices for "compassionate" purposes." All this makes even more difficult and dramatic the condition in which the doctor operates and promotes the emergence of speculative phenomena that exploit desperation and fuel easy illusions. Faced with such delicate situations, the NBC believes there must be provision for methods of judgment that reflect the complexity of the cases treated, by requiring that the therapeutic treatment does not come only from the attending physician, but it should receive the support of qualified specialists in the form of expressed authorization by a specifically dedicated panel, appointed by NHS institutions, and submitted to the approval of the Ethics Committee, under whose area of expertise the request pertains[26].

[26] For our country, cf. art. 4, paragraph 2 letter. a) Ministerial Decree 8 May 2003 entitled "Therapeutic use of investigational medicinal product".

In addition, the profession of a doctor is not limited to the administration of treatment. He has to monitor the progress of therapy, making from time to time appropriate assessments about the effects that the therapy has on patients. It also follows that the doctor must ensure the requirements of the traceability of the product and the patient treated and reported to the bodies deputed for this by the State for the clinical data on adverse events and the outcome of treatments carried out.

6. Conclusions

The dramatic nature of serious diseases for which there are no effective and validated treatments sometimes places those involved - patients, institutions, doctors - in tense situations if not, sometimes, in mutual opposition to the rights, duties, hopes and expectations of each. In the light of the reflections and considerations, the NBC believes that these situations can be addressed more adequately in accordance with the following guidelines:

1. It would be advisable to use a different term to "compassionate care", so as not to confuse it with legitimate feelings of empathy for patients with serious pathologies resulting in fatal outcome, very often children. The NBC in this regard suggests: "non validated treatments for personal and non-repetitive use" and calls for a "*consensus conference*" in order to adopt appropriate terminology that is shared internationally.

2. Such treatments are allowed in exceptional cases, when there is no validated therapeutic alternative in cases of urgency and emergency that put the patient's in mortal danger or serious rapidly progressive pathologies; they can not be an explicit or surreptitious alternative to clinical trials, nor can they by no means replace it.

3. The administration of these treatments must refer to specific indication and normally be based on multiple reasonable scientific evidence, namely: data published in specialized magazines with international circulation and "*peer review*" evaluation which include at least robust and evident results regarding animal testing for efficacy and toxicity and possibly with Phase I results on human beings.

4. This therapeutic prescription can not only come from the treating physician but must receive the approval of the Ethics Committee in whose area of expertise the request pertains. In addition the support of qualified specialists for the diseases for which compassionate treatment is requested is necessary preferably in the form of expressed authorization by the specific panel, designated by public health institutions called on to express an opinion in a short time. In the event that the patients concerned are minors these panels must provide for the presence of neonatologists or pediatricians with proven experience in the age group concerned.

5. It is necessary to avoid both conflicts of interest for those who are prescribing or administering or authorizing the treatment, as well as elements relating to possible speculation of an economic and industrial nature.

6. The composition of the products used for the treatments must not be secret, be they synthetic or biological in origin. All results both positive and negative must be made public.

7. Since it is a request for non-validated treatment, it obviously can not be binding on the physician.

8. For patients who want to have access to a “compassionate" therapy there must be the guarantee of receiving complete explanations on the potential dangers of this type of treatment.

9. The cost of the non-validated drugs normally must be borne by the manufacturer, while the relative monitoring must be headed by the specific facilities and public health institutions.

10. When the above mentioned points are complied with “compassionate” treatments are ethically licit and come under the general right to health.

A Personal Remark

Remark signed by Prof. Salvatore Amato and Prof. Assuntina Morresi

Hope is a risk worth taking (G. Bernanos)

The coordinators of a working group are responsible for examining in depth the issues related to the subject matter to be reflected on by the NBC, to collect all the positions, to prepare a written text that will form the basis of the future document and ... to step aside. To step aside if the majority decides to develop arguments, or even conclusions, other than those which they had initially hypothesized. In this sense, the opinion does not belong to the coordinators more than it belongs to every member of the Committee who, by voting it, has approved the contents. The reason for this short note is not in a disagreement with a text that we agreed upon with the great majority of my colleagues, but rather in the fact that two aspects of the problem of "compassionate treatment" have not seen an accentuation or declination which to us seemed essential. Ours is, therefore, a sort of "*concurring opinion*", for further adhesion to the document, reinforced by a few other considerations.

The first aspect and the most important, concerns the issue of freedom of treatment. The right to health has many facets, but it is undeniable that the freedom of treatment constitutes the central nucleus. Long quotations are not appropriate in an NBC document, but we believe they can find room in a "note", just to give an overview as complete as possible of the current debate.

Here for instance is what Amedeo Santosuosso writes: "Freedom of care is a fundamental right of every individual whether it is understood as an absence of the obligation to accept medical care, using any method effective or ineffective official or alternative. The ultimate expression of this freedom is the total refusal of health care, letting the disease take its course: this is the basis of every freedom and every right. The freedom to choose the method of health care is grafted onto this fundamental freedom[27].

It therefore appeared necessary to us to identify the problem of compassionate use of drugs surrounding the NBC opinion of *Refusal and conscious renunciation of health treatments in the patient-doctor relationship.* We did not want to claim that the " Stamina case" was a consequence of the right to refuse treatment but to reflect on the right that the individual has on his own body and if this right does not also include even a tragic and painful right to "self-experimentation". Some American states have recognized in extreme situations the existence of a "*right to try*" to be enforced even against pharmaceutical companies who denied the utilization of a drug not yet validated by the FDA.

So we take this opportunity to reiterate some of the concepts that unlike the majority of colleagues we deem necessary to describe more thoroughly the issue in question.

Although the aforementioned opinion *Refusal and conscious renunciation of health treatments in the patient-doctor relationship* does not explicitly touch on the problem of so-called compassionate treatment, however, it poses a number of important conditions that affect the evaluation of the patient's right to undergo non-validated treatment in the absence of an alternative. This document

[27] A. Santosuosso, *Un altro caso Di Bella?,* in “Minorigiustizia”, 2-2013, p. 250.

outlined several key points: the pre-eminence of informed consent" This document outlined several key points: the rule of informed consent "allowing the full valorisation of the choices made by the competent patient based on the principle of autonomy"; the right "to maintain control over what happens to one's body and one's life"; "the right obtain otherwise the realization of one's request for the termination of health care, even in consideration of an eventual or possible abstention by the doctor or medical team."

Here then we reiterate the question that in our view was partially circumvented: this right to decide what is good for oneself, in setting the parameters of one's "own" health, does it also entail a kind of right to self-experimentation, obtaining, without burdening the NHS service and with the endorsement of a prescription the administration of innovative therapies or even therapies without any adequate scientific evidence?

We are aware of the substantial difference that exists between the right to refuse healthcare treatments, which is based on "nothing on my body without my consent," meaning the "protection of the psychophysical freedom of a person whose bodily dimension must be respected" and instead the right to obtain, especially if not validated, a difference also emphasized in the opinion on "compassionate care".

Setting aside this issue - that of having to draw the boundaries of freedom of health care and the autonomy of informed patients - one may be faced with the following paradox, reiterated by some patients who have strongly requested access to compassionate treatments: a person suffering from a serious fatal disease that consciously decides to die, suspending life-saving treatment or artificial nutrition and hydration, would be entitled to do so, in the name of his own competence, autonomy and awareness, so as to demand its implementation of his wishes even if the doctor was opposed to this, by searching for other doctors. If the same person wanted to try to even just improve the quality of life, with the certainty of impending death, consciously taking responsibility for the risk of a non-validated treatment, his consent, competence, autonomy and awareness, along with the conviction of a doctor, would no longer have validity in the name of "safety" for his health, established by a regulatory authority.

We believe that so-called compassionate treatments are ethically permissible only within the strict framework identified in the opinion that we approved.

At the same time, however, we can not but think about the consequences that go with the freedom of treatment and patient autonomy, which inevitably result therefrom reconsidered within a perimeter determined by the appropriateness of treatments (defined according to objective and criteria) and the autonomy of the experts who reserve the final decision in this regard.

The second aspect that we believe we should integrate is the "right to hope," that we dealt with in the opinion because we were directly called upon to act by a number of judgments in the " Stamina case ", as well as in the literature in English. We do not believe that the plethora of rights that obsessively crowd legal texts and very debatable rulings should also include that of hope. But we think that in a paragraph entitled "on the side of the patient," the motivations of those who claim to have this right should be further discussed, to avoid falling into "bioethical paternalism" to the detriment of the completeness of representation of all the factors at play.

This is why we think it important to emphasize that this request comes from the fact that there is no doubt that patients are waiting for treatments, and are hoping for treatments. Hope is an existential attitude that includes in itself the wait, literally "expecting", it appears mostly as a "waiting" trustful in the help of science and medicine respecting the schedule and rules of scientific research. But hope, even in the motivation, may lead to taking personal risk by virtue of a positive personal attitude, a desire to pursue a glimpsed opportunity, in the conviction that a solution may exist, for example, along not validated or experimented paths.

The "right to hope", in this perspective, therefore means the personal right to taking a risk in view of a possible positive solution (where the category of "possible", is different from that of "probable" in a statistical sense: "possible" means that it can happen even just once, even if it has never happened before, and it is not reasonable be exclude it occurring, while "probable" indicates a measured and quantified certainty based on events that have happened or however are foreseeable according to models).

Even in this case resort to a long quotation to emphasize how this view is widely held in literature and in doctrine, therefore the Committee should have considered it in quite a different manner.

On the reasons that justify compassionate treatments Cendon writes: "... they appear dictated (to recall the vocabulary used by the Italian and European legislator, by judges, and doctrine, in these matters) by consideration on pietas, solidarity, humility, benevolent spirit, lack of alternatives, conjectural availability, mercy, therapeutic realism, comparative pragmatism, human understanding, in relation to individual cases"[28].

We believe that the expression "right to hope" arises from this position, and not from a feeling albeit respectable but - implicit - that is totally irrational and unfounded; and it is this position entirely that has to be dealt with and responded to, without censorship. For this reason we agree with the appropriate definition of hope given by G. Bernanos "hope is a risk worth taking", in the framework of reasonableness identified by the approved opinion, outside of which it would not be a question of hope, but of cruel illusion.

[28] P. Cendon, *Cellule staminali somministrate ai bambini sofferenti di gravi malattie neurologiche*, in "Minorigiustizia", 2-2013, p. 236.

ATTACHMENT:

A JURIDICAL NOTE

1. In Italy, the legal framework is based on Article. 32 of the Constitution that guarantees health as a "fundamental right of the individual and collective interest." This right, however, is divided into a plurality of positions, characterized by content and intensity of the different protection.

The administering of new drugs and their marketing are a key aspect of this right. They are, therefore, subject to statutory regulation imposing the requirement of a preliminary ministerial authorization. The treatments and cures that fall within this category and that are regularly provided have passed through all the stages of testing and have obtained approval by the scientific community regarding their innocuousness and effectiveness. In the context of validated drugs those which fall within the category LEA category (Essential Levels of Care) should be guaranteed throughout the national territory in conditions of equality for all persons (citizens and non-citizens) and be free of charge or shared charge, after that is, payment of the prescription charge (Law 537/1993).

Therefore, the present case of so-called compassionate treatment is outside the therapeutic practices generally regulated. There are, however, exceptions to the ordinary institutional forms of administration of drugs or other therapeutic treatments tested.

Firstly to be mentioned, although dated is, the Legislative Decree 178/1991, which aimed at establishing the areas of legislation *de qua*, and provided for certain exemptive situations: in paragraph 7, letter. b) it gives the doctor the option to request the national or foreign production of medicines to be administered at his own responsibility to the patient prior to regulatory approval and for a period not exceeding thirty days. The rule is still vague in that it does not make explicit the conditions for which the doctor is authorized to request treatment outside the rules, thereby marking a strong discretionary power of the doctor in assessing the most appropriate treatment for the patient, including also compassionate treatment

More detailed regulation regarding compassionate treatment and reimbursement by the NHS is deductible by Law no. 648, 23 December 1996 (the result of conversion of Decree Law no. 536/1996). Under Article. 1, paragraph 4 of the law, where there is no valid therapeutic alternative it may be dispensed fully charged to the National Health System: a) innovative medicines on the market in other States, but not in Italy; b) medicinal products not yet authorized, but undergoing clinical trials; c) medicines to be used for a therapeutic indication different from the one approved; all included in a special list drawn up and regularly updated by the Committee on the Safety of Medicines in accordance with the procedures and criteria adopted by the same committee.

In this regard, however, the limited scope of the provisions has been clarified. The Committee on the Safety of Medicines has noted that "falling outside the scope of the quoted norm is the treatment restricted to individual patients, following an assessment of their specific medical conditions, with registered medicinal products for other therapeutic indications. In such circumstances, assignable to the situation governed by Article. 3, paragraph 2 of the Decree-Law 17 February 1998, no. 23 converted with amendments, into

Law 8 April 1998, no. 94, charges are borne by the patient in accordance with paragraph 4 of that Article. It is understood that the use of the medicine for the benefit of a patient admitted to a public or private accredited facility is borne by the National Health Service, since the hospitalization fee is inclusive of the cost of the administered pharmacological treatment[29].

Also of relevance is the regulation of the use of *off-label* drugs, the provisions of which, in addition to in the Law 1996 no. 648, are chiefly contained in the law April 8, 1998, no. 94 (Conversion Law Decree 17 February 1998 no. 23).

For *off-label* drug use refers to, for the purposes of the aforementioned legislation, the use of drugs: a) for therapeutic indications other than those contained in the marketing authorization; b) given in different doses to those contained in the instruction form of the medicine; c) to persons included in different age groups to those which are commonly prescribed.

If in general, the doctor, when prescribing a medicinal product, must follow the therapeutic indications and the mode of administration provided by the marketing authorization issued by the Ministry of Health, the 1998 Law no. 94 provides a number of exceptions to this principle, giving the doctor a degree of autonomy, accompanied by a corresponding individual responsibility. In exercising that autonomy, the professional must always refer to a set of criteria relating to the accuracy and adequacy of his professional work. In particular, the doctor can legally prescribe an *off-label* drug only in the presence of three competing requirements: 1) inability to effectively treat the patient "*in-label*"; 2) obtaining the informed consent of the patient; 3) compliance with the *off-label* drug use in relation to articles that have appeared in accredited scientific publications, even at international level[30].

In this regard, it should be remembered that the Code of Medical Ethics, in its latest version (2014), indicates partially equivalent conditions: the doctor may prescribe medications for indications or dosages not covered by the data sheet, if their safety and efficacy is supported by science and the risks are proportionate to the expected benefits; in such cases it justifies activity, acquiring the written informed consent of the patient and assessment of the effects in time[31].

The “compassionate use" is reflected in Ministerial Decree May 8, 2003 "Therapeutic use of drugs undergoing clinical trials." It provides for the possibility of use of a medicinal product in the pharmaceutical facility authorized or regularly imported, which is undergoing clinical trials in Italy or abroad, for a

[29] This is press release 04.07.2002 on the scope of Article. 1, paragraph 4 of Decree Law October 21, 1996, no. 536, converted by Law 23 December 1996, no. 648.

[30] Article. 3 co. 2 of Law 94/1998 states that 'the doctor may, under his direct responsibility, and after informing the patient and obtaining the consent of the same, use a medicine manufactured commercially for an indication or means of administration or a method of administration or use different from the one authorized or recognized to the effects of Article. 1, co. 4th of Decree October 21, 1996 n. 536, converted into Law 23 December 1996 n. 648, if the doctor thinks, based on documented data, that the patient can not be successfully treated with medicines already approved for that therapeutic indication or that means or method of administration and provided that such use is known and is in conformity with articles that have appeared in scientific publications accredited internationally."

[31] The seventh paragraph of art. 1 of the Council of Ministers 2014 states: "The doctor can prescribe drugs not registered or authorized for trade or for indications or dosages not covered by the data sheet, if their safety and efficacy is supported by science and the risks are proportionate to the expected benefits; in such cases it justifies activity, acquiring the written informed consent of the patient and assessment of the effects in time."

use outside of experimentation, in the case where there is no valid therapeutic alternative to the treatment of serious pathologies, or rare diseases or life threatening disease conditions. Under Article. 2 of the law two conditions must still be complied with: a) that the product is already the subject, in the same specific therapeutic indication, of experimental clinical trials, ongoing or concluded, or in the third phase or, in the particular cases of life threatening diseases, in clinical studies already completed or in the second phase; b) that the available data of the trials referred to in a) are sufficient to formulate a favourable opinion on the efficacy and tolerability of the drug.

When these requirements are met it is also envisaged that the pharmaceutical manufacturer sees to the supplying of the free of charge of the drug (paragraph 3 of art. 4 of the Ministerial Decree). The medicine can then be requested: a) by the doctor for nominal use on a single patient not treated in clinical studies (individual compassionate use); b) by multiple doctors; c) by doctors or collaborative groups for patients who have participated in a clinical trial demonstrating an efficacy and tolerability such as to represent a need, for the same patients, to benefit at the earliest opportunity from its findings (group compassionate use).

The manufacturing company may provide the medicine on the basis of a protocol upon which there are documented among other things the clinical grounds for the request, the data on efficacy and tolerability, the procedures for informing and patient consent. The protocol should also be submitted by the doctor (who however bears the responsibility) to the approval of the relevant ethics committee which can also operate by urgent procedure and forwarded to the Office for Research and Clinical Trials of the Italian Pharmaceutical Agency that, where appropriate, may issue a suspensory opinion on the procedure or use.

The supply of the material by the producer is subject to the favourable opinion of the ethics committee.

A form of accountability due to violation of the Protocol is provided for in Article. 22 of Decree Law 211/2003 implementing Directive 2001/20 / EC which, however, merely provides for administrative liability of a pecuniary nature.

Considering specifically advanced therapy medicinal products reference must be made to the decree "Turco-Fazio" (Ministerial Decree 5 December 2006): *Use of drugs for gene therapy and somatic cell therapy outside of clinical trials and transitional norms for production of such medicinal products,* followed by the decrees for extension of 18 December 2007 and 24 December 2008.

Under this regulation gene therapy medicinal products and somatic cell therapy can be used on individual patients subject to certain conditions, given by the lack of valid alternative therapies, in case of urgency and emergency in which the patient's life is in danger or damage to health and in the case of serious rapidly progressing diseases (art. 1 co. 4). Also in this case the doctor prescribes this treatment under his own direct responsibility while, as regards the quality of the medicine, the responsibility is borne by the director of the production plant laboratory. The prescription of these drugs and therapies can take place only when: 1) there is available scientific data to justify its use (published in accredited international journals); 2) the informed consent of the patient has been acquired; 3) the favourable opinion of the ethics committee has been acquired concerning the relationship between the hypothesised benefits and foreseeable risks in relation to the patient's condition; 4) in the case where the medicine has been produced by laboratories in possession of

the requirements contained in Art. 2 and however in compliance the pharmaceutical quality requirements approved by the competent authorities, while, if the drug has not been tested in Italy, there must be ensured respect for the requirements of pharmaceutical quality approved by the Institute of Health; 5) treatment should be carried out in institutions of in-patient care of a scientific nature, or equivalent public facility.

Since 2009, D. L. 219/2006 has entered into force (implementing Directive 2001/83 / EC and 2003/04 / EC) regulating advanced therapy medicinal products used in individual patients. Art. 3 paragraph 1, f-bis[32] states that such therapy should be prepared in non-industrial scale and that it must be administered in a hospital, only for a particular patient and under the responsibility of a doctor. This "*custom made*" regime, called "*hospital exemption*" in Article 28 of EC Regulation 1394/2007, represents even in Italy a derogation from the requirement of actual marketing of the product. In addition, treatment is outside the scope of a clinical trial according to DL 211/2003.

Italy has implemented what is indicated by the aforementioned EC Regulation 1394/2007 without further specifications, if not specifying that the preparation of the products under the regime of "*hospital exemption*" must be authorized by AIFA.

Initially The criteria for the authorization of the law for their use were subsequently established with the decree signed on 16 January 2015 (which will be described later).

The Decree Law March 25, 2013 , n. 24 (*Provisions on health*) , converted into Law 23 May 2013 , no. 57 [33], has made possible , even after some favourable rulings in this sense , the Stamina treatment, intended as compassionate treatment, only in cases in which the treatment had already begun (Art. 2).

A provision that has raised the question of unconstitutionality, with reference to Arts. 2, 3 and 32 of the Constitution on inviolable rights , the right to healthcare and the equal dignity of all citizens, from the Ordinary Court of Taranto, part of the lawsuit filed by a patient who asked to be allowed to be subjected to treatment for the first time. The Constitutional Court, with judgment 274/2014 of 5 December 2014, declared that the question of constitutional legitimacy of art. 2. According to the Court, "decisions on the merits of therapeutic choices, according to their appropriateness, could not arise from assessments of pure policy discretion by the legislator, but should provide for the elaboration of guidelines based on verification of the state of scientific knowledge and acquired experimental evidence , through institutions and organizations - typically national and supra-national - delegated to this, given the vital importance that to these purposes technical and scientific bodies play. "

Moreover, according to the Court, the promotion of a clinical trial of a new drug does not allow as a rule , to charge in advance to public facilities the administration of the drug itself: for obvious reasons of health protection, as well as requirements for proper use and destination of the funds and resources available to the NHS.

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[32] Lett. F-bis introduced in D. L. 219/2006 by the paragraph 1 of article. 34 of Law 88/2009 (Community Law). Further modified with the Decree Law March 4, 2014, no. 42 (Implementation of Art. 1, paragraphs 1, 5 and 12 of Directive 2012/26 / EU amending Directive 2001/83 / EC as regards pharmacovigilance).

[33] Conversion into law , with amendments, Decree-Law of 25 March 2013, no. 24 , concerning urgent provisions on health matters

However, the Court noted that in the present case, the legislature of 2013, in giving course to a trial on the use of advanced therapy medicinal products based on mesenchymal stem cells, although it has partially waived the principles set out above , it did so intervening in the particular factual situation that saw, concretely, that treatment had already begun with stem cells at the initiative of several judges who, as a precautionary measure, had ordered it to be carried out in public facilities.

An effect of the most recent Decree Law no. 36 of 2014 (converted into Law no. 79 of 2014) has been a change to the Law no. 648 of 1996 with the addition in Ch. II (Use of less expensive medicines by the National Health Service) Art. 3-bis, paragraph 1.4 that allows the dispensing of medicines to be used for a therapeutic indication other than that authorized by the SSN, even if there is another therapeutic alternative in the context of authorized products. Even in this case, with the approval of AIFA, these medicines must be entered in a proper register, and they may be used provided their use is known and conforms to research conducted as part of the medical and scientific community nationally and internationally, within the parameters of affordability and appropriateness.

On 16 January 2015 the Ministerial Decree was signed "Provisions relating to advanced therapy medicinal products prepared on a non-repetitive basis" limited to advanced therapy medicinal products prepared on a non-repetitive basis. The Decree provides inter alia that: the production and use is authorized by AIFA; that producers comply with the rules on quality and safety , and traceability of the product and the patient treated and pharmacovigilance; use can only take place in a public hospital , teaching hospital or institution of in-patient care in of a scientific nature , of individual patients , in the absence of a valid therapeutic alternative , in cases of urgency and emergency when the patient is in a life threatening situation or serious damage to health; use takes place under the professional responsibility of the doctor made pursuant to an individual medical prescription for a custom-made product for an individual patient , after informed consent and approval of the Ethics Committee; the results must be assessed by the Institute of Health and AIFA. The decree states that the AIFA should evaluate the application for authorization of production within 60 days and the application for authorization of use within 30 days.

2. Also with regard to the compassionate use of medicines, the important role played by the Code of Medical Ethics (2014) must be remembered. In general terms, the text defines for the doctor the duties related to the protection of life and physical and mental health, to pain treatment and alleviation of suffering, while respecting the freedom and dignity of the person and without any discrimination (art. 3). The cardinal principle of the therapeutic relationship, which has a key role, is informed consent that can form a real alliance between doctor and patient; it is the condition for the full valorisation of self-determination and freedom of the person in relation to the choices concerning health. The prescription of a therapeutic treatment or medication is the exclusive competence of the doctor, who intervenes under his direct responsibility following a circumstantial diagnosis.

Although in relation to the specific case, it must take into account the scientific evidence available, subject to the guidelines accredited by authoritative and independent sources.

The doctor must therefore base his activities on the principles of clinical efficacy, safety and appropriateness, monitoring the effectiveness of the treatment on the individual patient.

On this basis, the latest version of the code of medical ethics includes some provisions that may have a specific application in terms of compassionate treatment. The last paragraphs of Article. 13, sets out, first of all that the doctor "can prescribe medication not yet registered or authorized for sale if their tolerability and efficacy is supported by science and the risks they are proportionate to the expected benefits; in such cases it motivates his actions, the acquiring of the written informed consent of the patient and the evaluating the effects in time." Under his direct responsibility, moreover, the doctor may prescribe "drugs that have passed only the phases of experimentation related to safety and tolerability, in strict compliance with the legal system". Still, it should be noted that the professional " does not agree to the request for a the prescription by his patient solely in order to please him," and does not adopt or spread "diagnostic or therapeutic practices for which there is no appropriate scientific and clinical documentation available that is assessable by the professional community and the competent Authority." Along the same lines, the doctor "should not adopt or spread secret therapies." In reference to unconventional treatment, as applicable within the context of compassionate treatment, art. 15 of the same Code adds that the doctor "should not withdraw his patient from treatments which are scientifically based and of proven efficacy."

The action which remains within framework just outlined is therefore licit, and falls within the sphere of autonomy and responsibility recognized to the doctor as part of his professional expertise.

3. With regard to the so-called compassionate use of medicinal products in the international context the Declaration of Helsinki should be considered which, although not strictly legal nor binding (having been adopted by the World Medical Association), has over the years come to be a model of reference for the entire medical profession. Article. 37 of the Declaration allows for intervention not tried, under the responsibility of the doctor and with the informed consent of the patient , when there are no other known treatments or interventions have proven to be ineffective and after having sought the opinion of experts[34].

In the European context regarding compassionate use for individual patients who have not participated in the clinical trial of the medicinal product in question (individual compassionate use), Directive 2001/83 / EC (the European Parliament and of the Council of 6 November 2001 Community code relating to medicinal products for human use, and implemented in Italy by Legislative Decree no. 219/2006) provides in Article. 5 that an EU Member State, in accordance with its law and to fulfil special needs, may provide medicinal

[34] Art. 37. Interventions unproven in clinical practice: "In the treatment of an individual patient, when there are no proven treatments or other interventions known have not proven effective, having sought the opinion of experts, doctor with the consent the patient or his legal representative, may use an unproven intervention if according to his judgment that the drug may be a hope to save life, restore the physical integrity or alleviate the suffering of the patient. This intervention should subsequently be made as the object of study, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and made publicly available when appropriate."

products not yet on the market in response to *a bona fide unsolicited order*. These medicines must be formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients under his direct personal responsibility. Also in this, in addition to the personal assumption of responsibility of the individual professional, the referral to state legislation implies the necessary presence of scientific literature related to the efficacy and the exclusion of toxicity of the product.

The expression "compassionate use" can be traced in art. 83 of EC Regulation no. 726/2004 , that authorizes individual states to derogate from the Community rules for the marketing of drugs in the event that a group of patients with a chronic, seriously debilitating or life-threatening illness, that can not be treated satisfactorily with an authorized medicinal product.

The objectives of Article. 83 are:

- to facilitate and promote access to compassionate use for patients in the European Union;

- to promote a common approach regarding the conditions of use , the conditions for distribution and the patients targeted compassionate use;

- to increase transparency between Member States regarding the availability of treatments.

Among the conditions laid down[35], in addition to the exclusive reference to the "group of patients who have already participated in the clinical trial of the medicinal product" (group compassionate use), the requirement that the medicinal product must be subject to an application for authorization to 'placing on the market or in any case be subjected to clinical trial[36].

Said EC Regulation. 726/2004 was amended by Regulation no. 1394/2007. The latter introduces for the first time the definition of "advanced therapies", including not only gene therapy and somatic cell therapy, as well as tissue engineered products. The main innovations introduced by the Regulation include: the establishment of an expert committee (Committee for Advanced Therapies), within the European Medicines Agency (EMA); the adoption of new requirements for quality, safety and traceability of the donation, procurement and control; the adoption of new regulatory procedures for classification and certification; support for small and medium businesses with incentives to promote entrepreneurship.

In addition, Regulation stipulates that each Member State should standardize the production and use of advanced therapies for individual

[35] The conditions are further detailed in the document "Guidelines on compassionate use of medicinal products, Pursuant to Article 83 of Regulation (EC) No 726/2004. Doc. Ref. EMEA / 27170/2006 "European Agency for the Evaluation of Medicinal Products (EMEA), now called the European Medicines Agency (EMA).

[36] Article. 83 of the Regulation that "= 1. Derogation from Article 6 of Directive 2001/83 / EC, Member States may make available for compassionate use, a medicinal product for human use belonging to the categories defined in Article 3, paragraphs 1 and 2 of this Regulation. = 2. For the purposes of this Article, for compassionate use we shall mean the making available, for humanitarian reasons, a medicine belonging to the categories defined in Article 3, paragraphs 1 and 2, to a group of patients with a chronic or seriously disabling illness or whose disease is considered potentially lethal, and that cannot be treated satisfactorily with an authorized medicinal product. The medicinal product concerned must be the subject of an application for marketing authorization under Article 6 of this Regulation or must be undergoing clinical trials. = 3. Where a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency [European Agency for the Evaluation of Medicinal Products]."

patients, treated in national public facilities, and therefore not aimed at placing on the market and commercialization.